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Uchiyama

(10) **Patent No.: US 9,476,849 B2**
(45) **Date of Patent: Oct. 25, 2016**

(54) **BIOSENSOR SYSTEM AND METHOD FOR MEASURING CONCENTRATION OF ANALYTE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 481 days.

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(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
G01N 27/327 (2006.01)
C12Q 1/00 (2006.01)

(52) **U.S. Cl.**
CPC ***G01N 27/3274*** (2013.01); ***C12Q 1/004*** (2013.01); ***C12Q 1/006*** (2013.01)

(58) **Field of Classification Search**
CPC G01N 27/00; G01N 33/483
USPC 436/150, 149
See application file for complete search history.

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Assistant Examiner — Emily Berkeley
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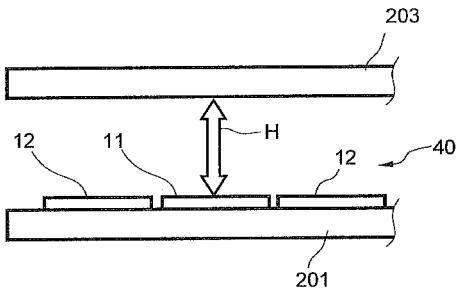
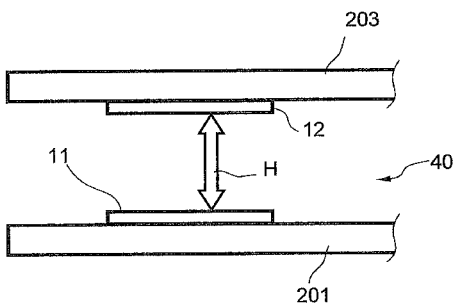
(57) **ABSTRACT**

A biosensor system can comprise a sensor chip and a measurement device. The sensor chip comprises a capillary and electrodes disposed within the capillary. The height of the capillary is set to be less than the maximum value of the sum of the diffusion distance of an electron-transfer mediator and the diffusion distance of an analyte at the upper limit of the measurement guaranteed temperature of the biosensor system. The measurement device applies an open circuit voltage, a voltage that is lower than during concentration measurement, or the like to the electrodes of the sensor chip.

9 Claims, 69 Drawing Sheets





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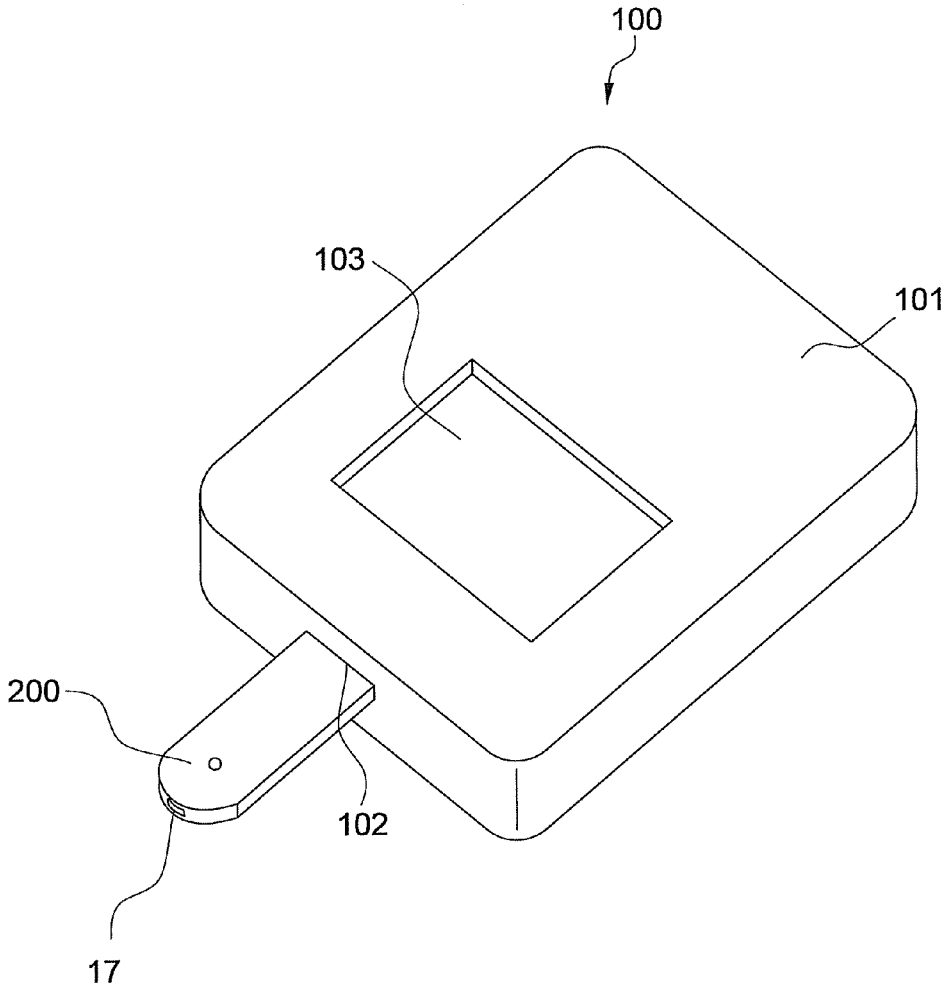


FIG. 1

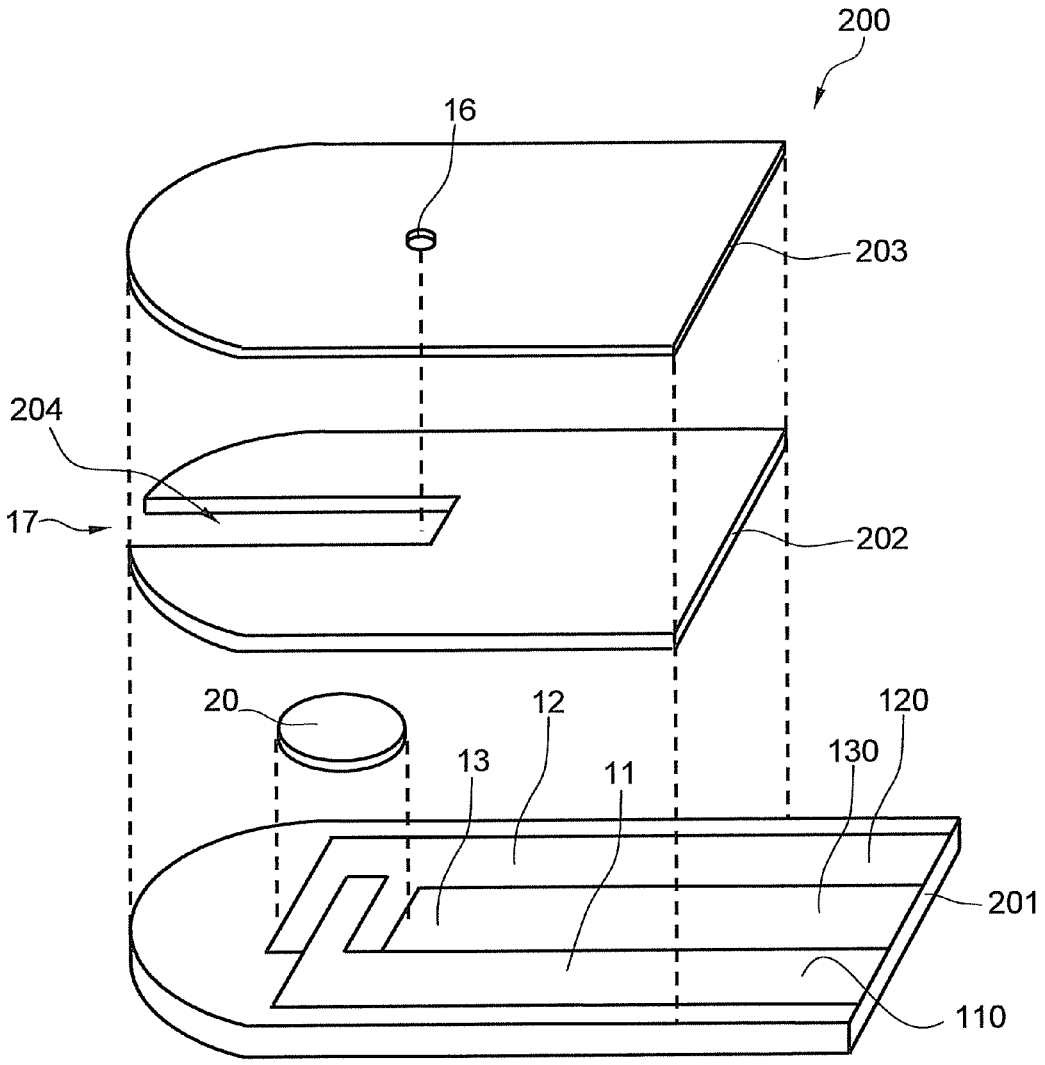


FIG. 2

FIG. 3

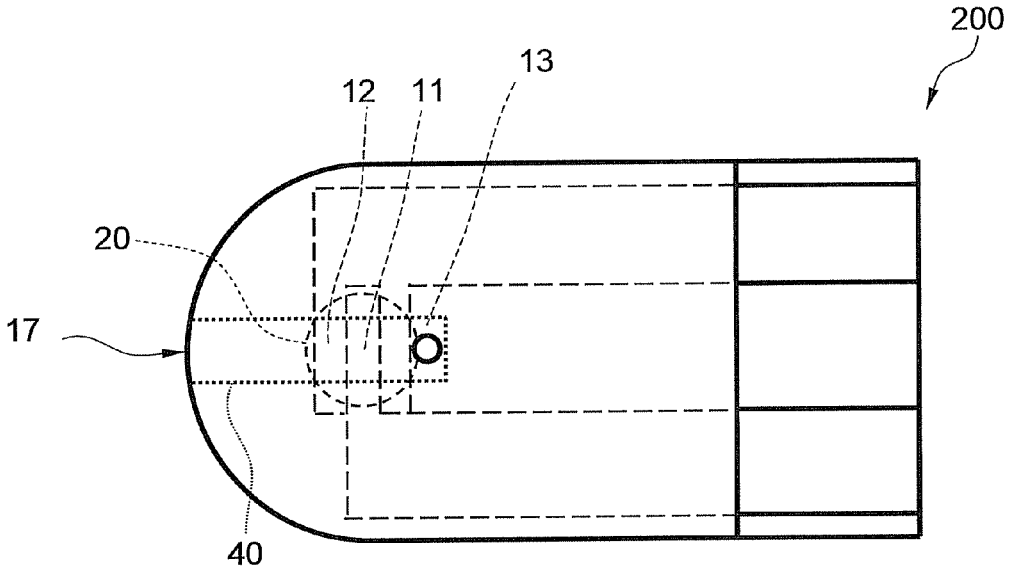


FIG. 4

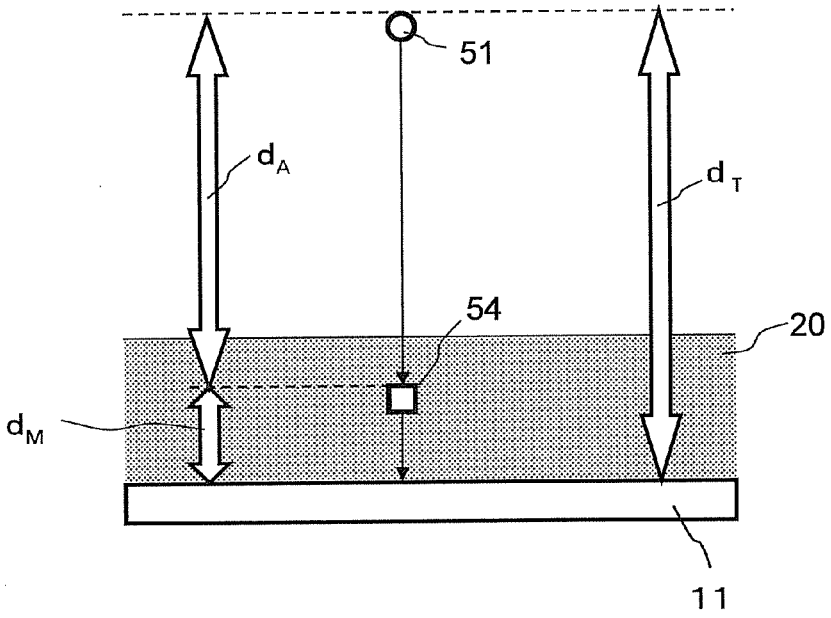


FIG. 5A

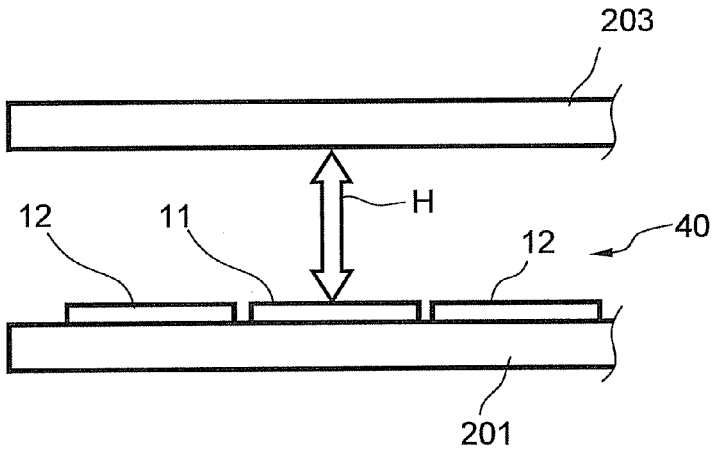
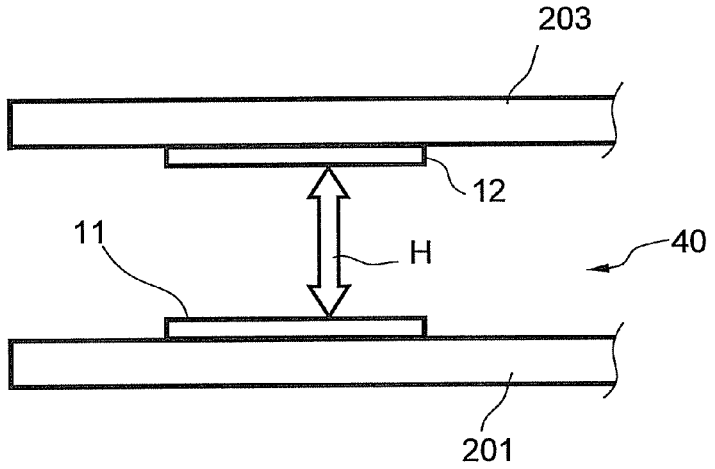


FIG. 5B



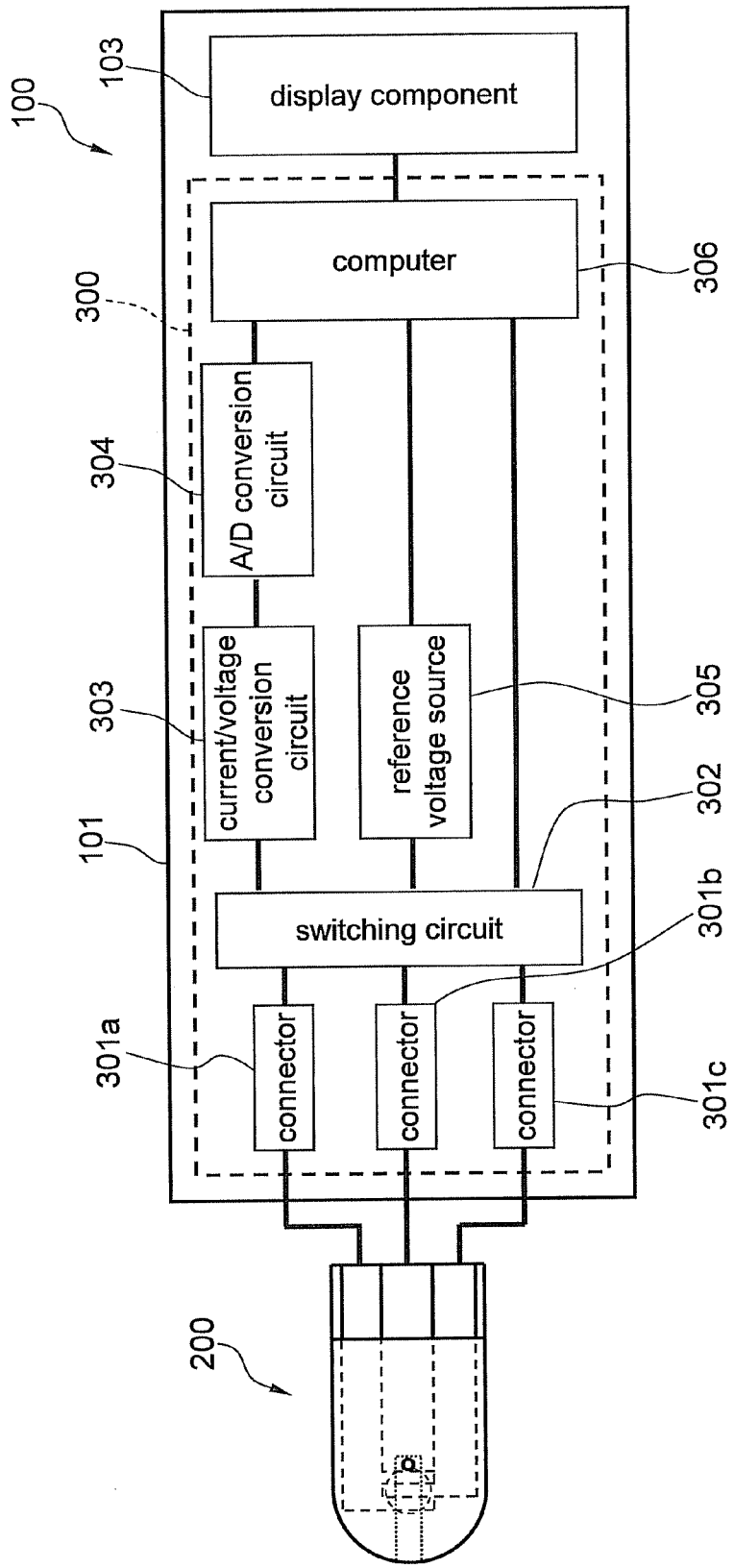

100
103
display component
computer
306
300
304
A/D conversion circuit
303
current/voltage conversion circuit
reference voltage source
305
302
101
switching circuit
301b
301a
connector
connector
connector
301c
200

FIG. 6

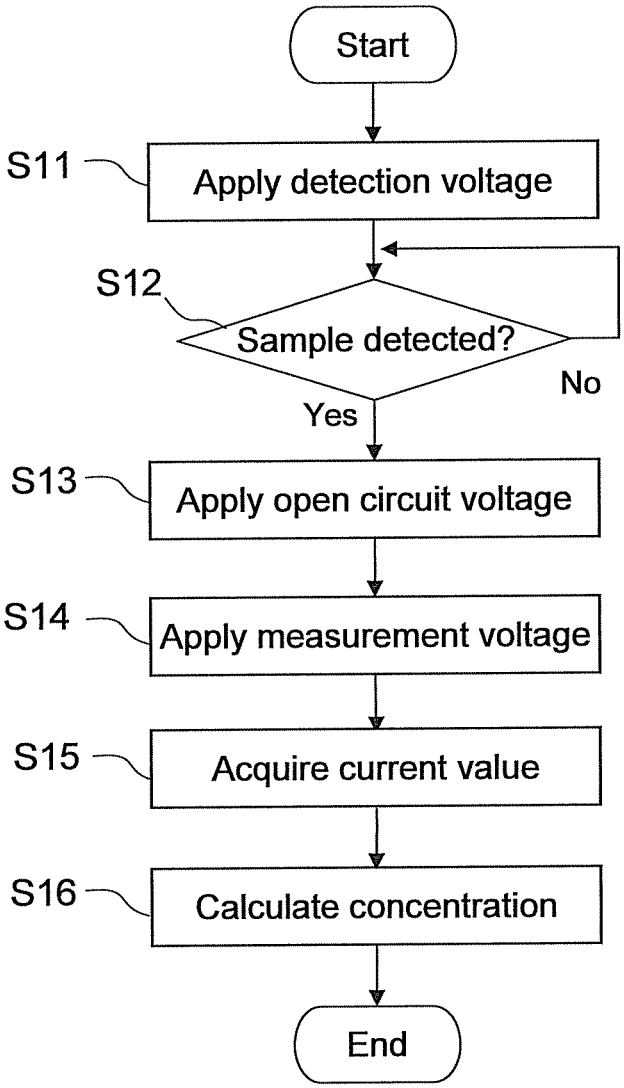

Start
S11
Apply detection voltage
S12
Sample detected?
No
Yes
S13
Apply open circuit voltage
S14
Apply measurement voltage
S15
Acquire current value
S16
Calculate concentration
End

FIG. 7

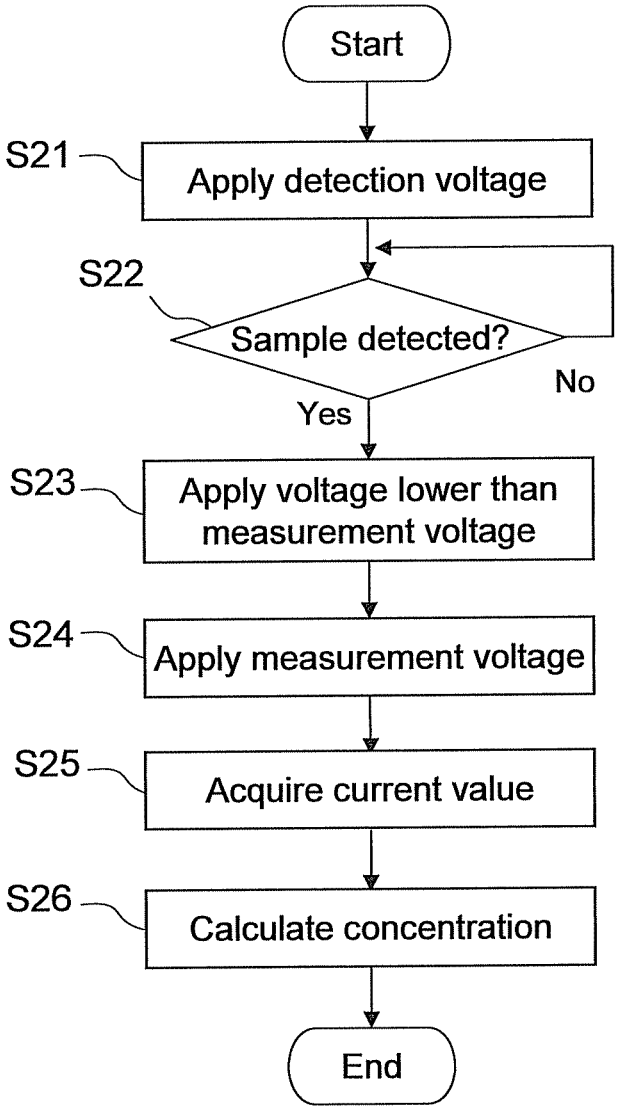

Start
S21
Apply detection voltage
S22
Sample detected?
No
Yes
S23
Apply voltage lower than measurement voltage
S24
Apply measurement voltage
S25
Acquire current value
S26
Calculate concentration
End

FIG. 8

FIG. 9

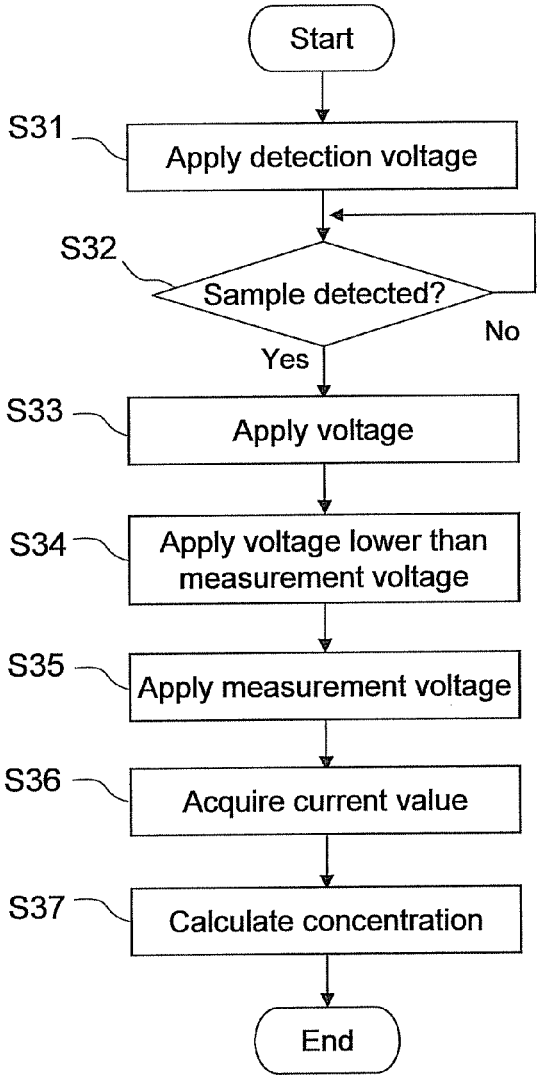

Start
S31
Apply detection voltage
S32
Sample detected?
No
Yes
S33
Apply voltage
S34
Apply voltage lower than measurement voltage
S35
Apply measurement voltage
S36
Acquire current value
S37
Calculate concentration
End

FIG. 10A

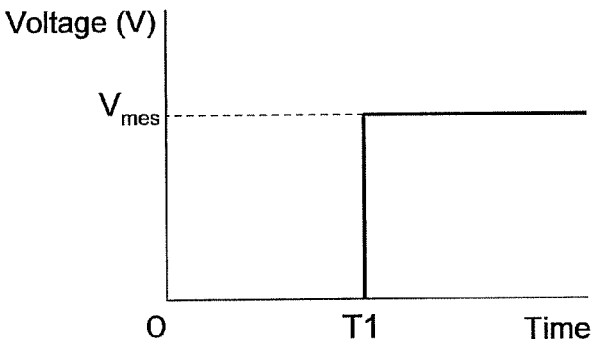

Voltage (V)
V_{mes}
0
T1
Time

FIG. 10B

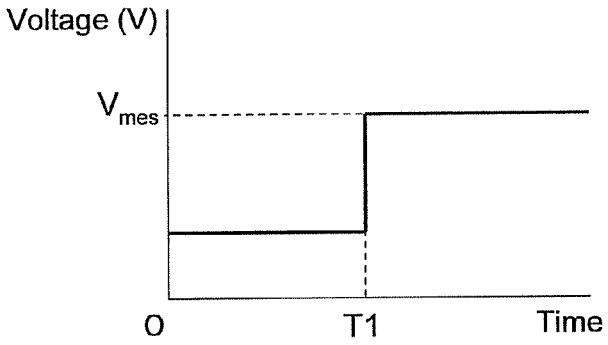


FIG. 10C

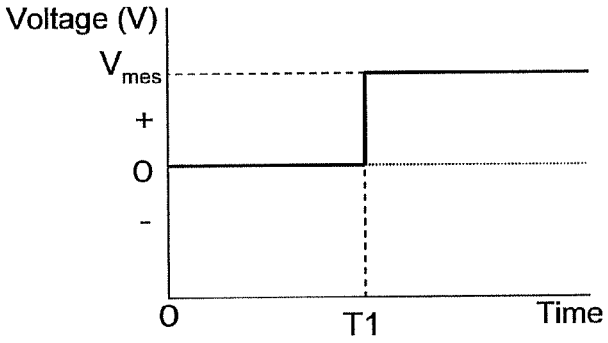


FIG. 10D

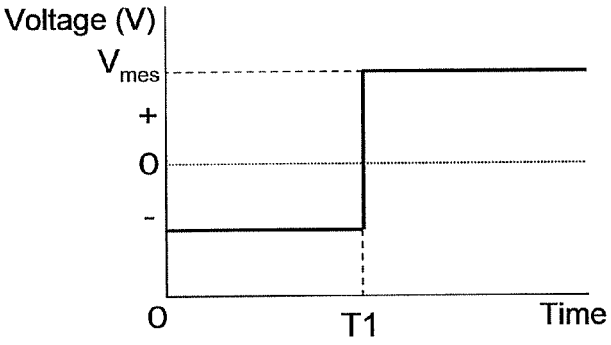


FIG. 11A

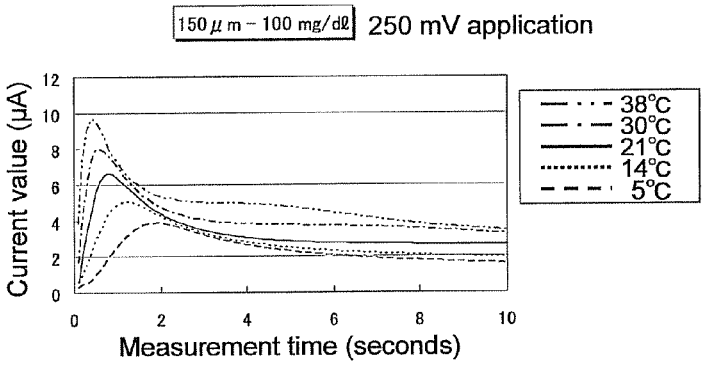


FIG. 11B

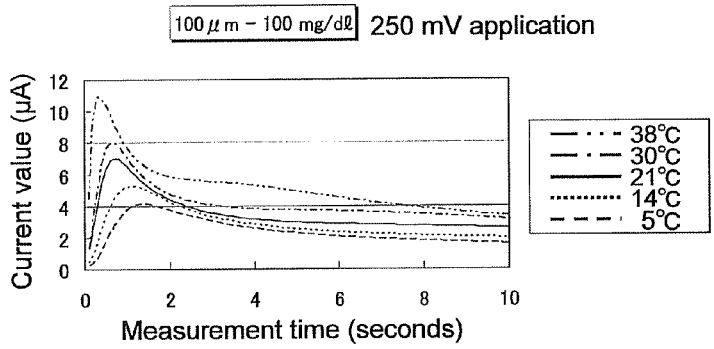


FIG. 11C

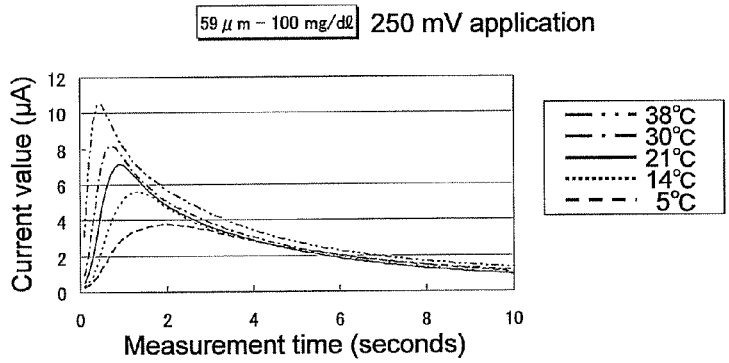


FIG. 11D

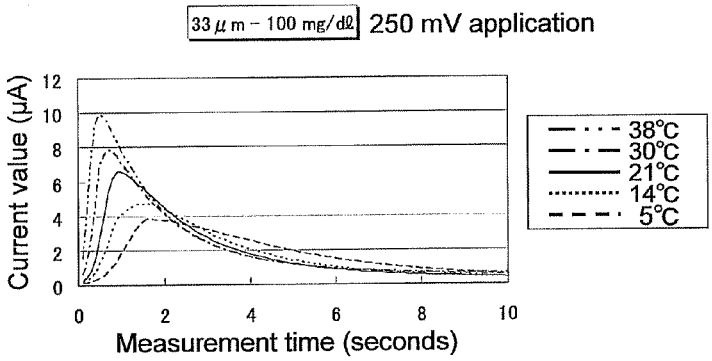


FIG. 12A

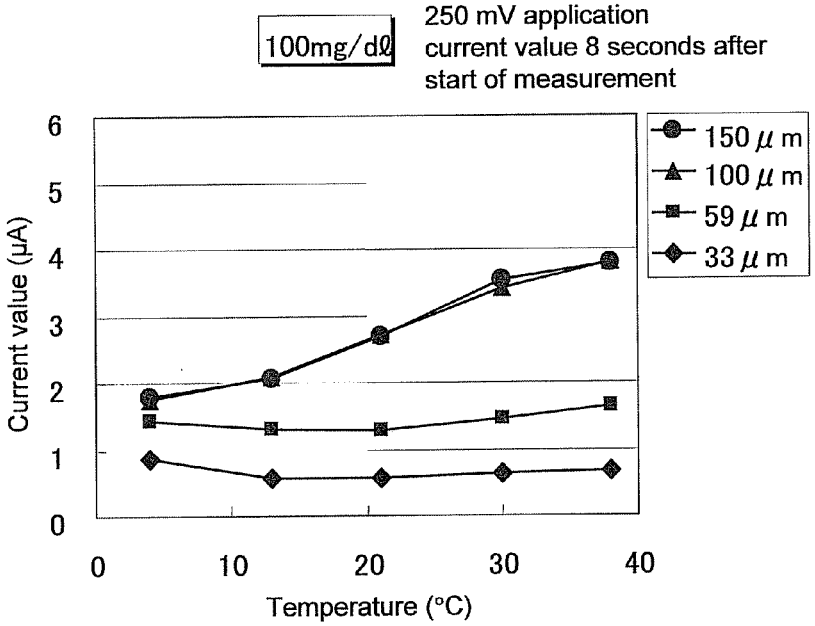


FIG. 12B

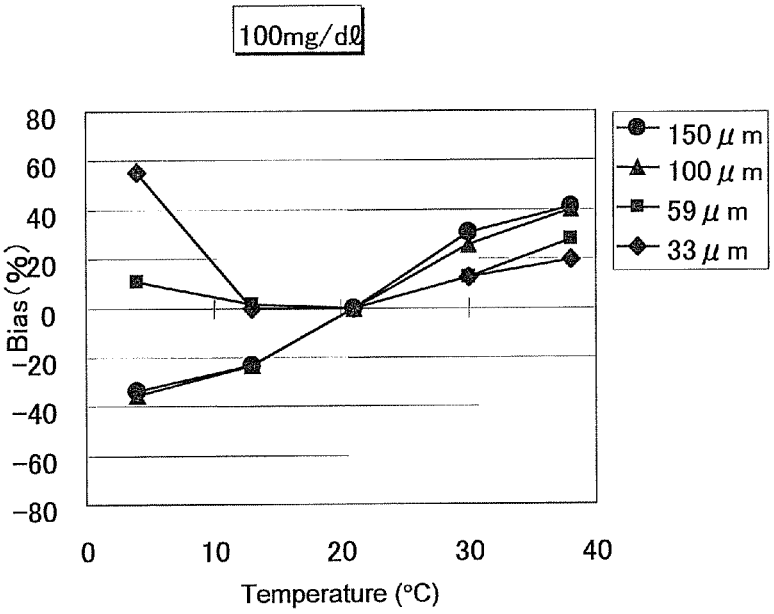


FIG. 13A

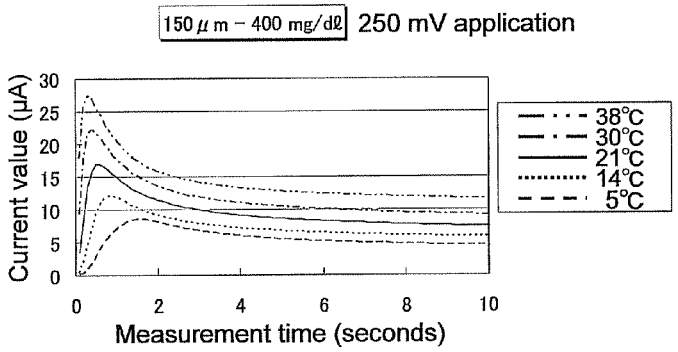


FIG. 13B

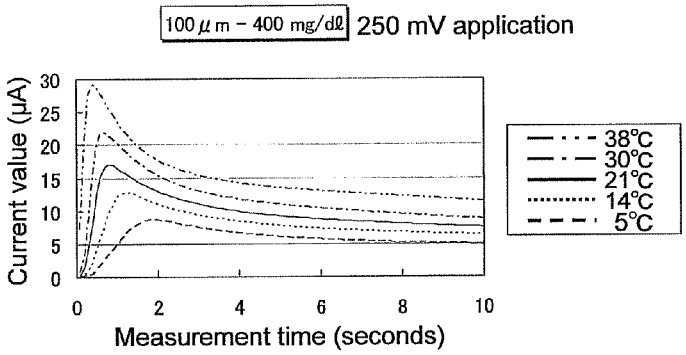


FIG. 13C

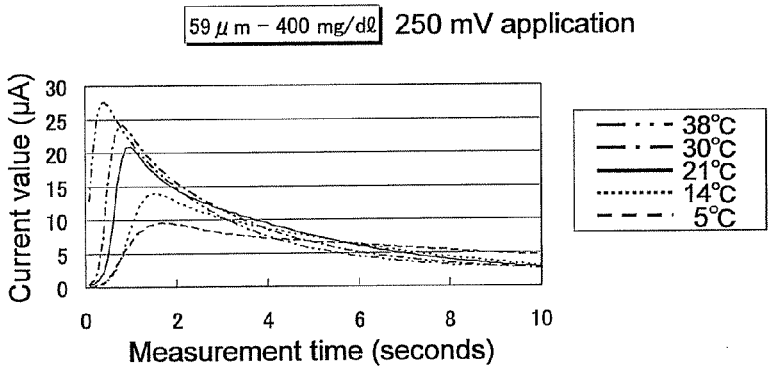


FIG. 13D

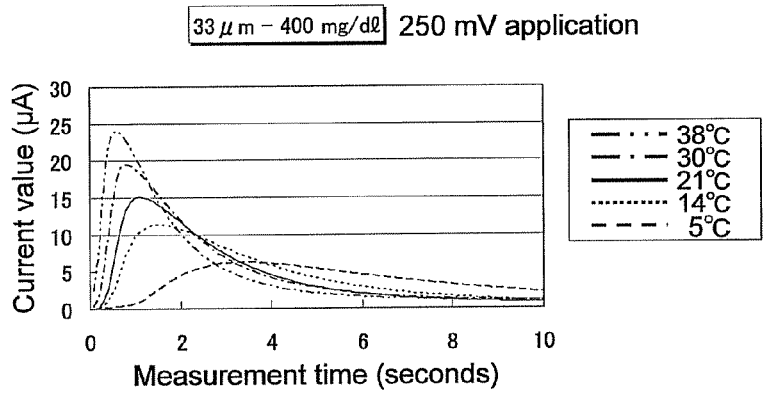


FIG. 14A

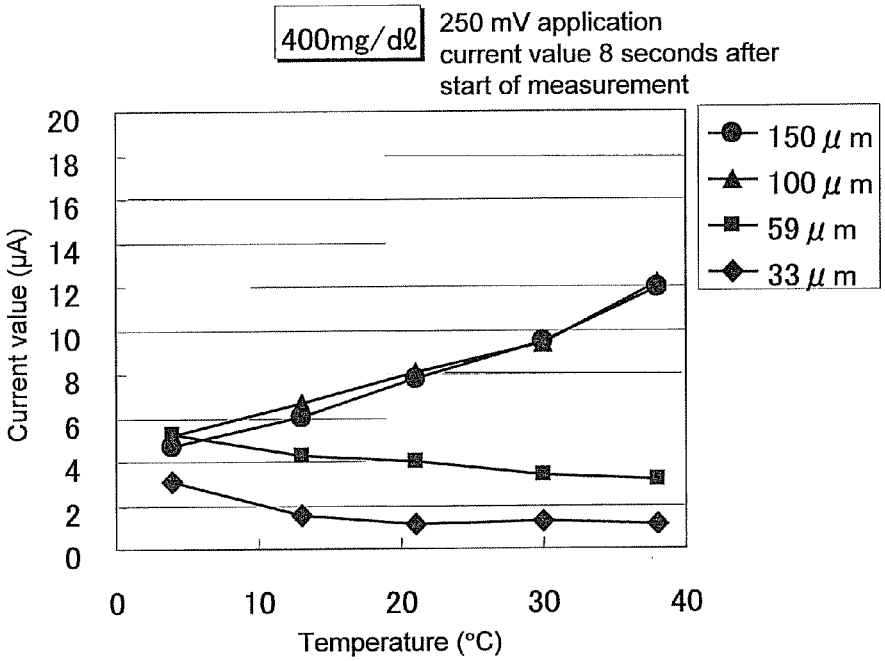


FIG. 14B

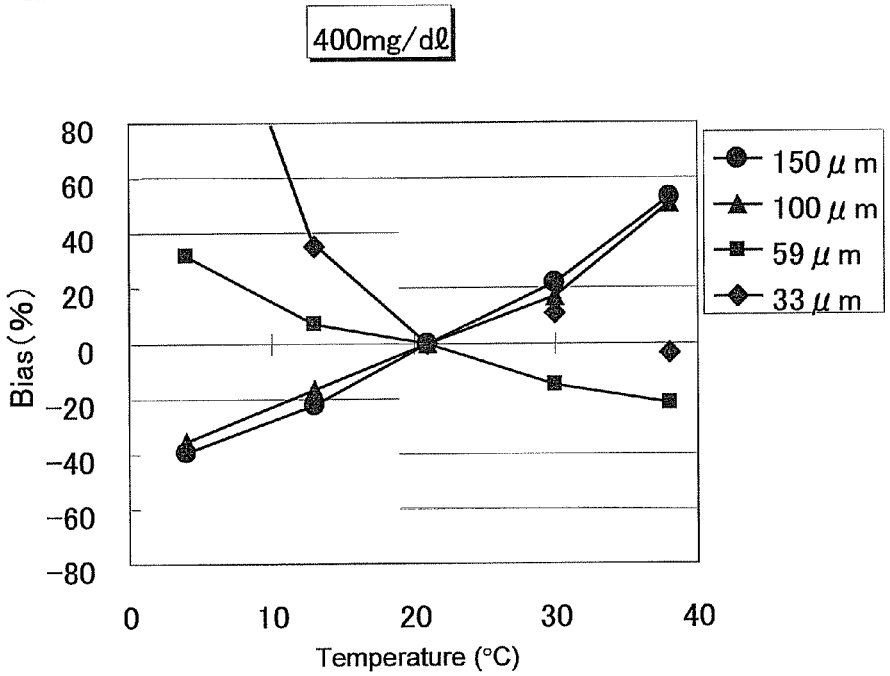


FIG. 15A

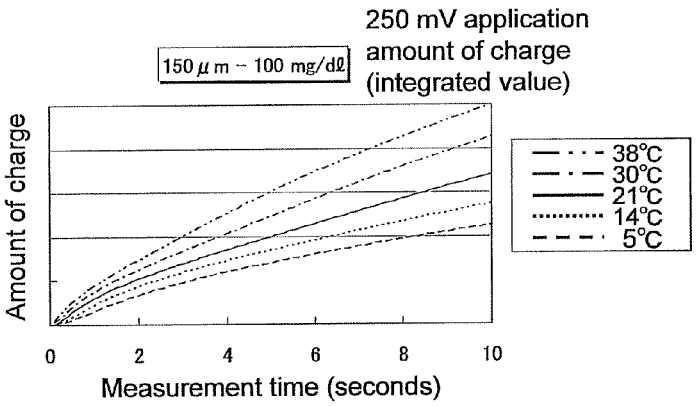


FIG. 15B

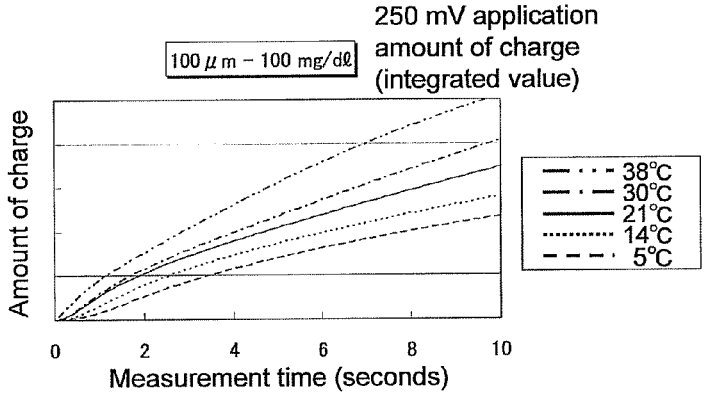


FIG. 15C

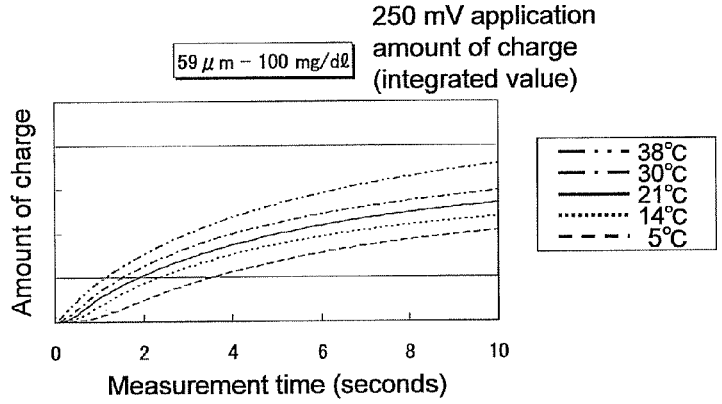


FIG. 15D

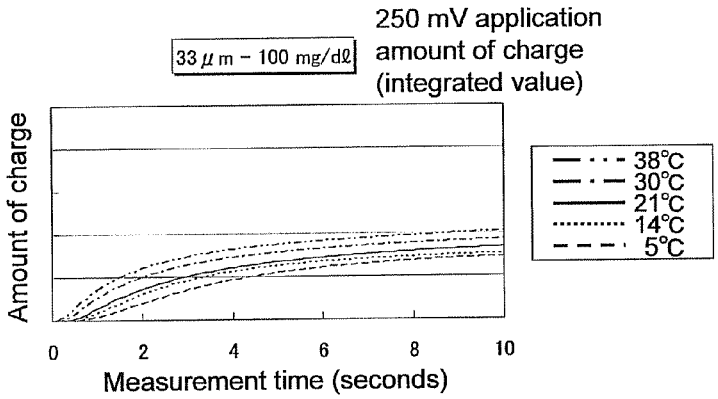


FIG. 16A

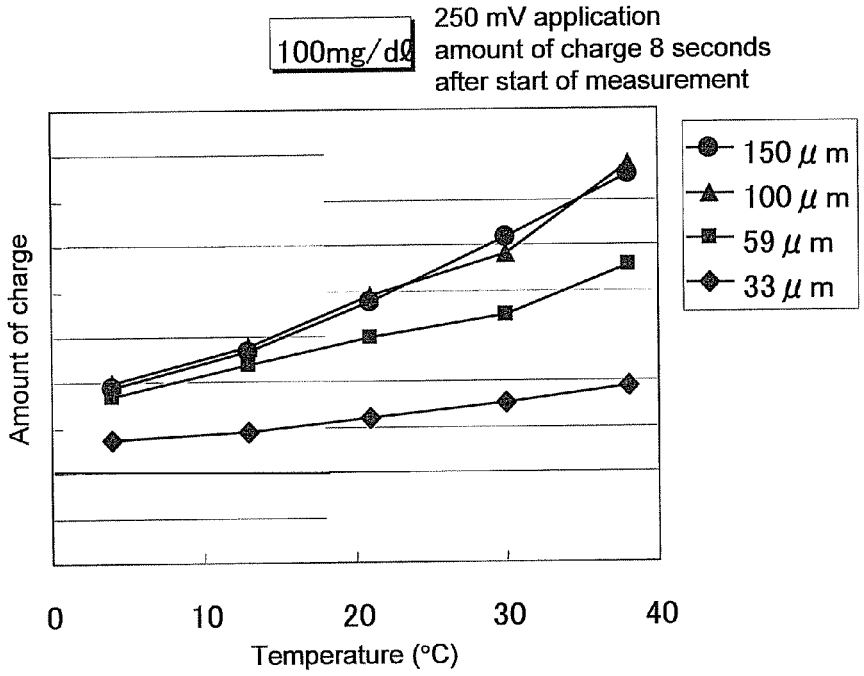


FIG. 16B

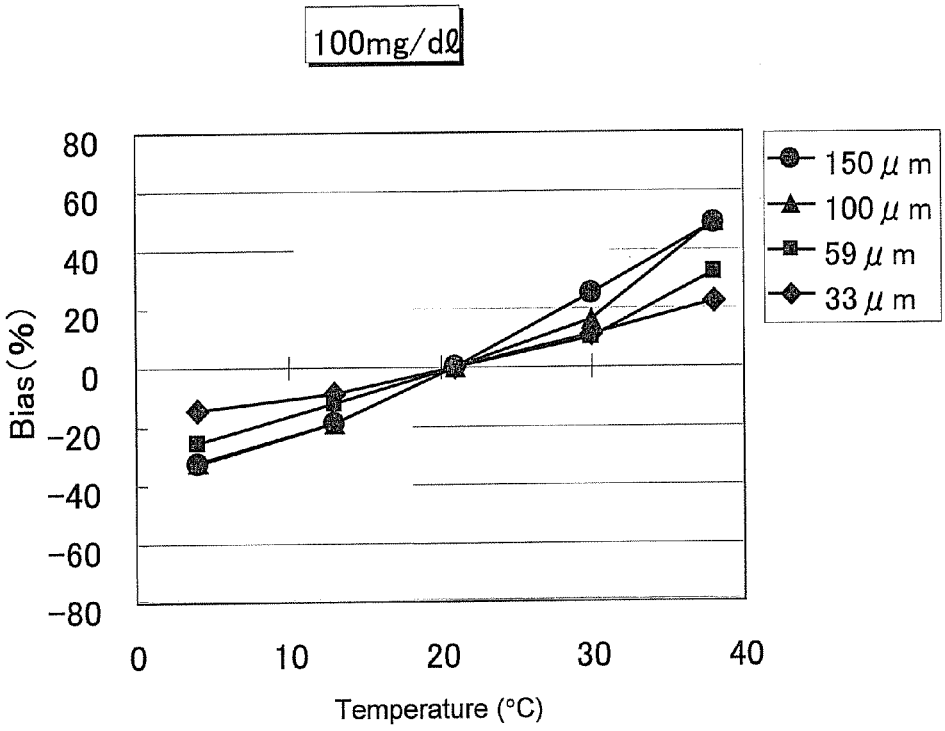


FIG. 17A

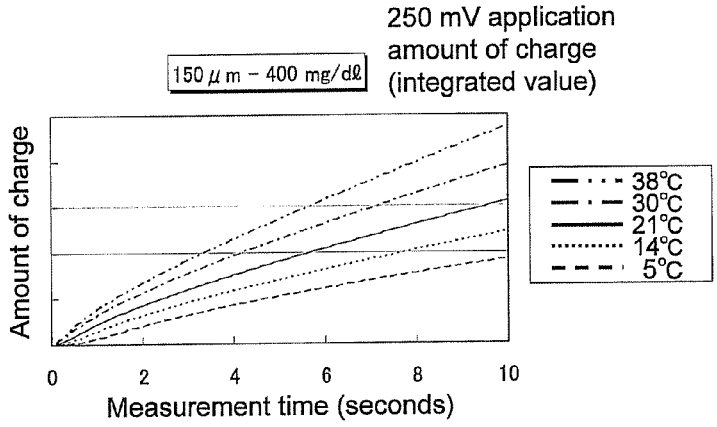


FIG. 17B

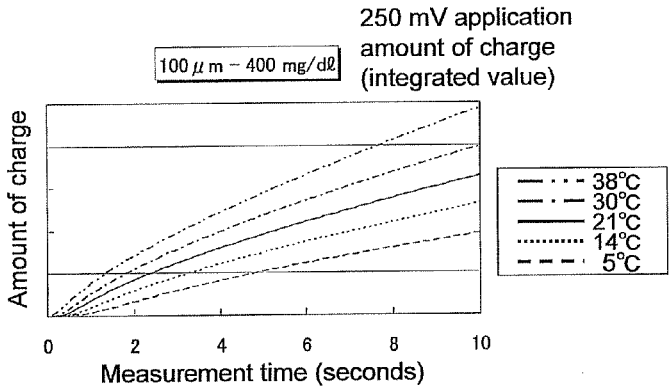


FIG. 17C

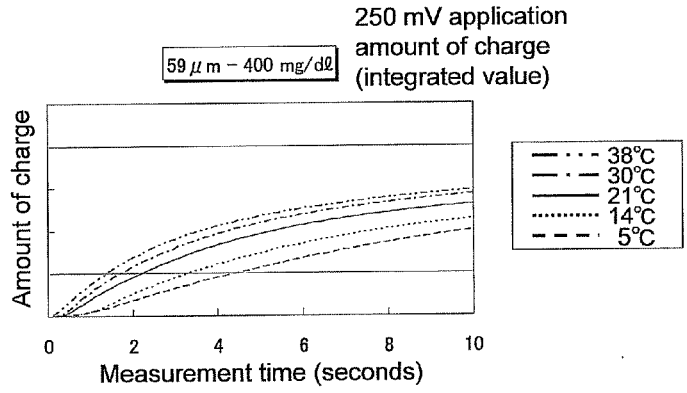


FIG. 17D

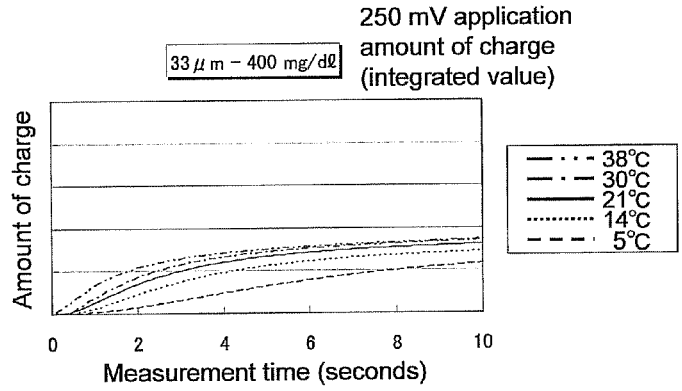


FIG. 18A

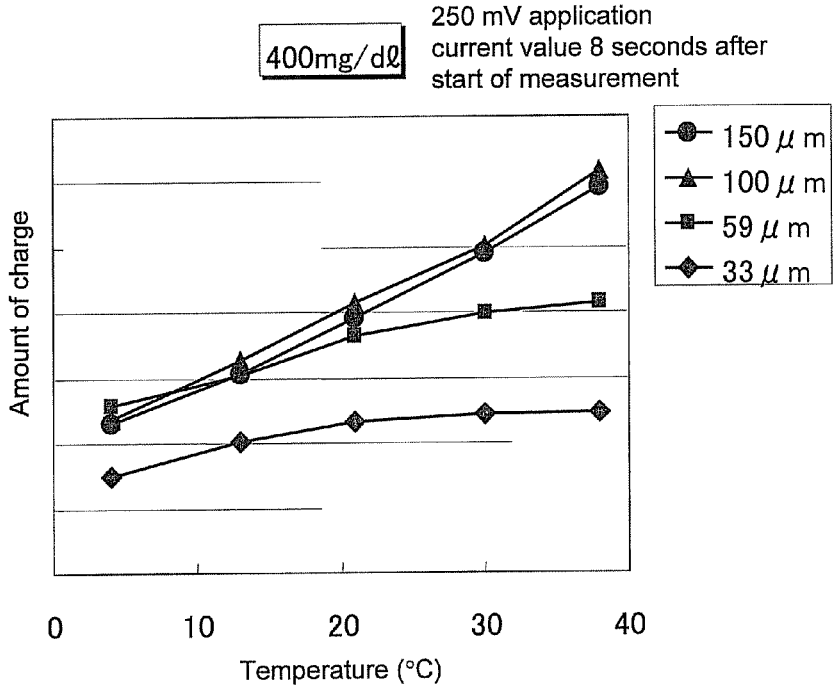


FIG. 18B

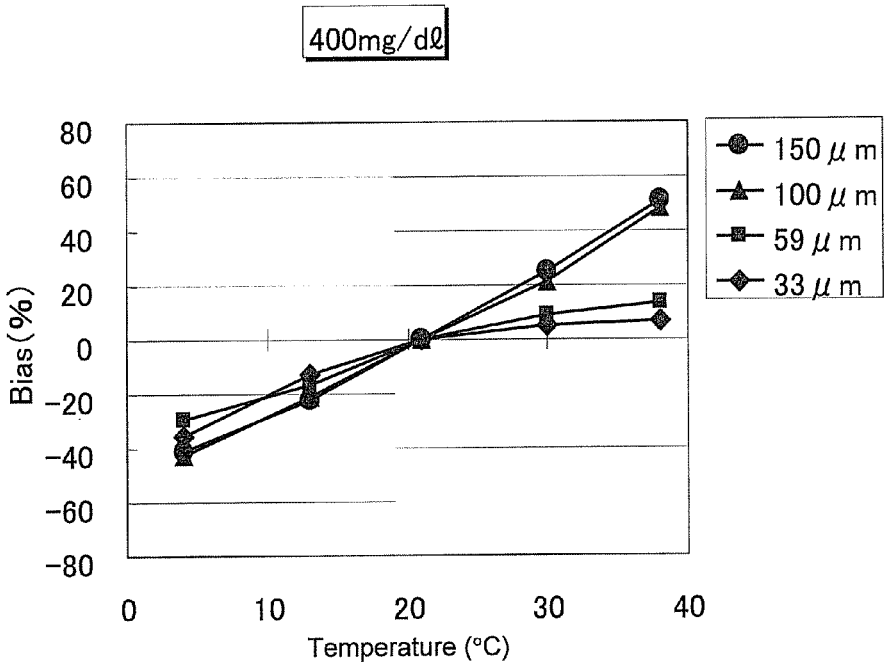


FIG. 19A

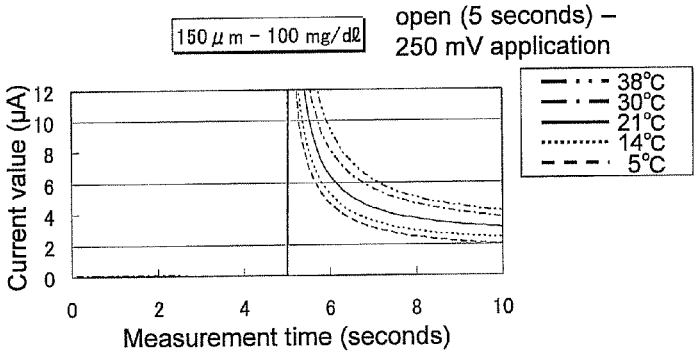


FIG. 19B

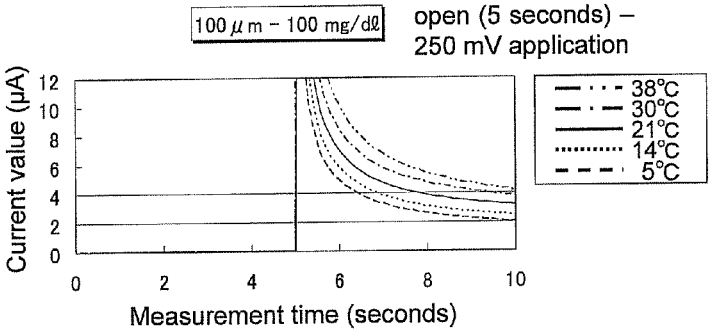


FIG. 19C

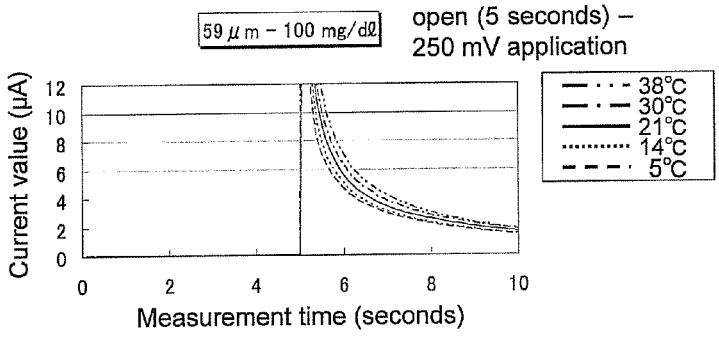


FIG. 19D

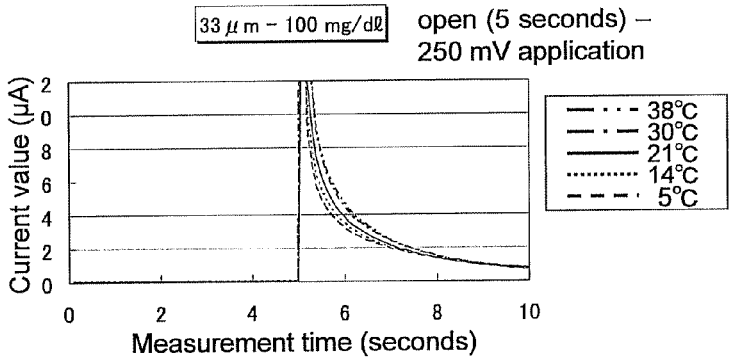


FIG. 20A

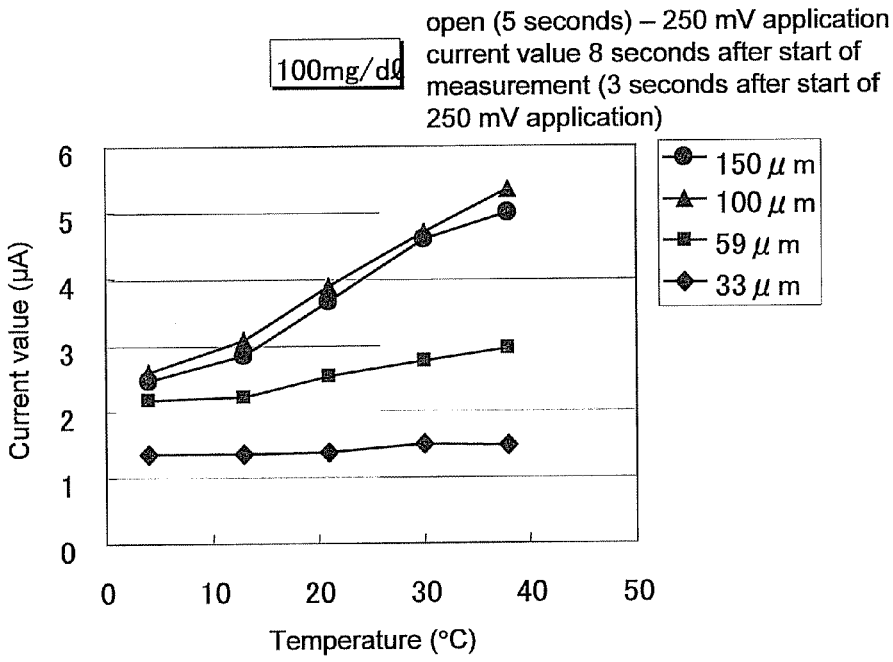


FIG. 20B

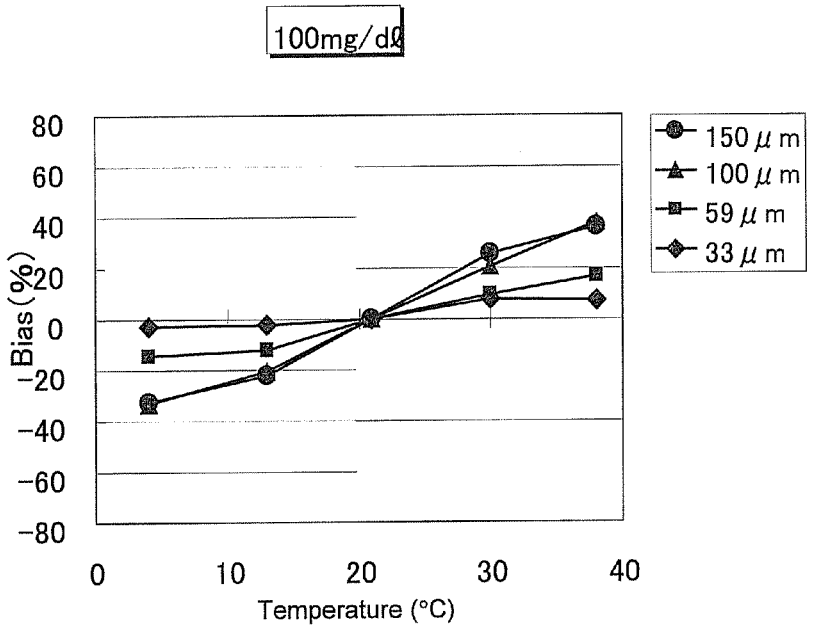


FIG. 21A

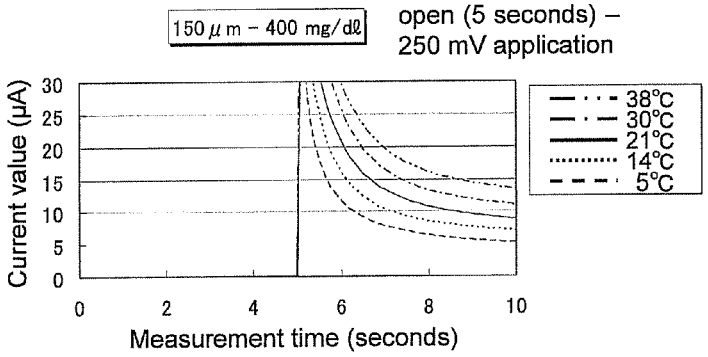


FIG. 21B

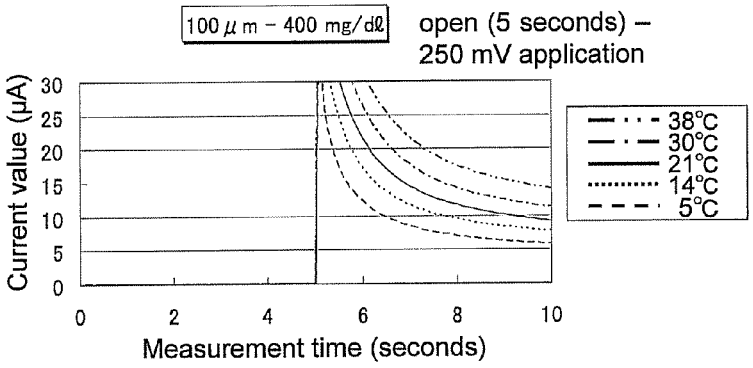


FIG. 21C

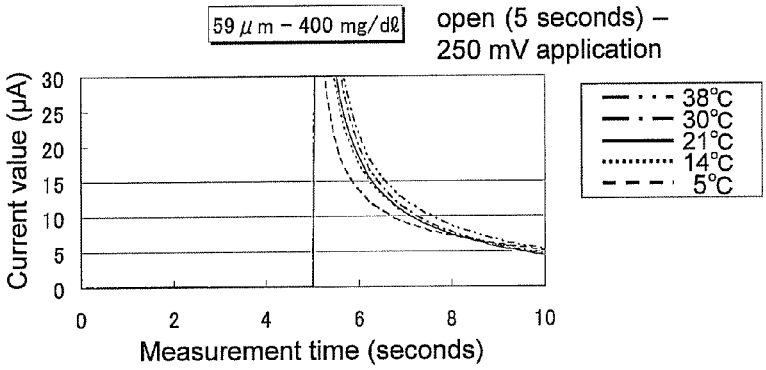


FIG. 21D

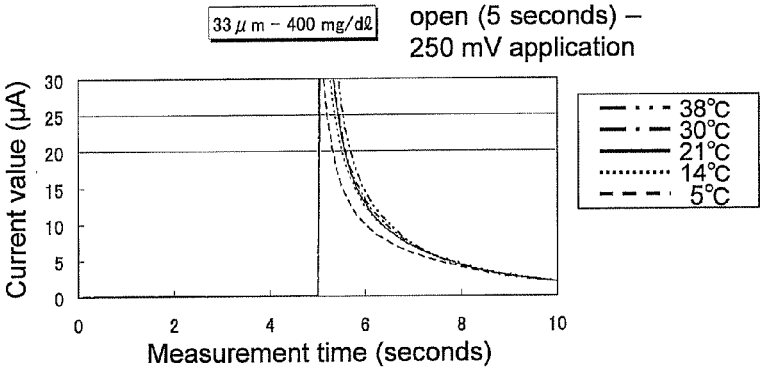


FIG. 22A

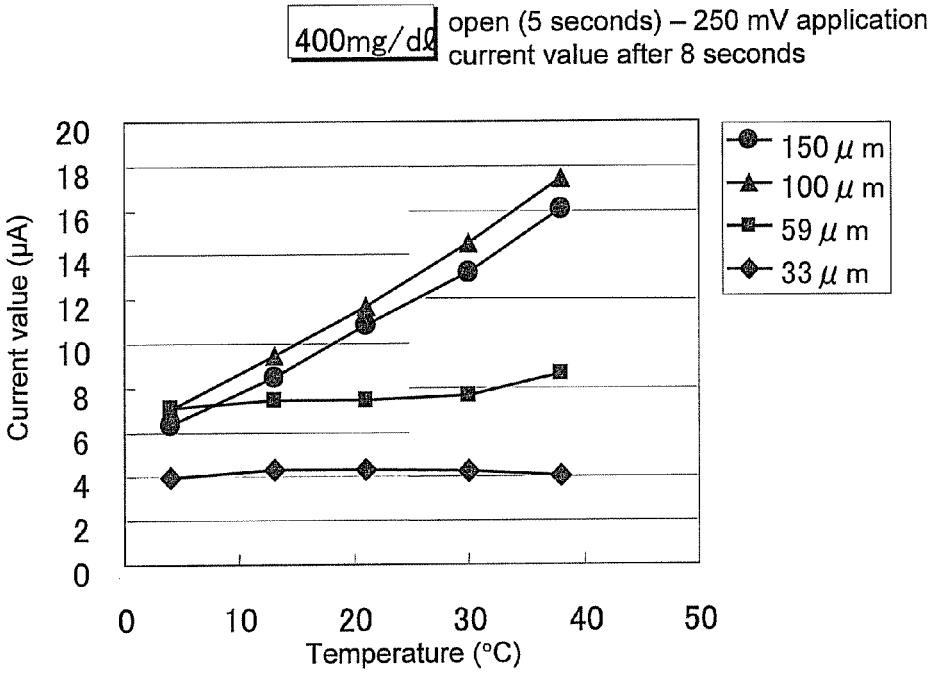


FIG. 22B

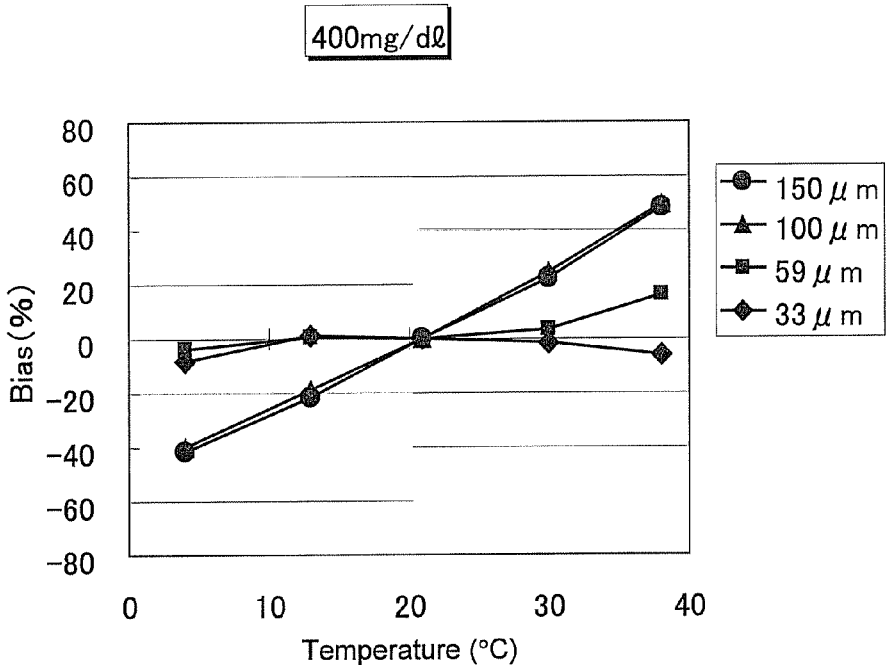


FIG. 23A

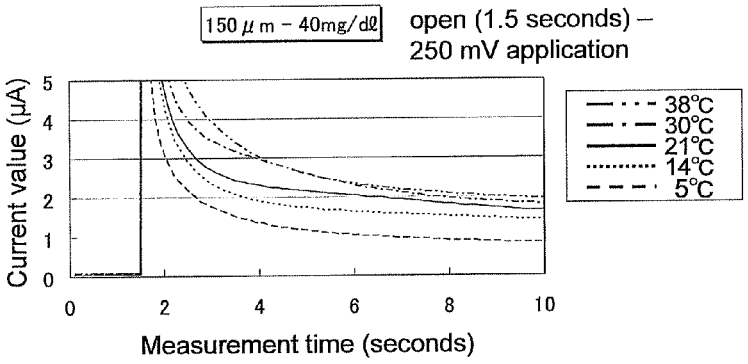


FIG. 23B

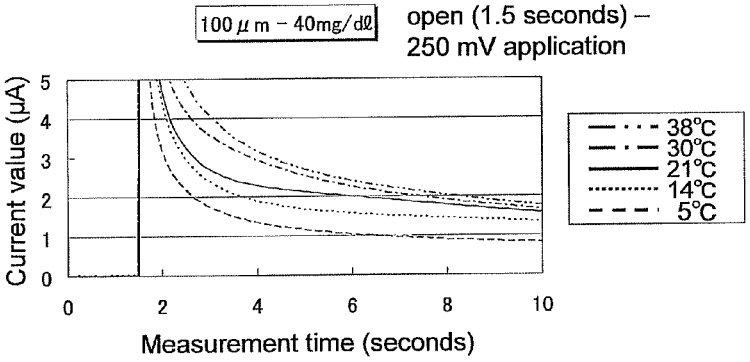


FIG. 23C

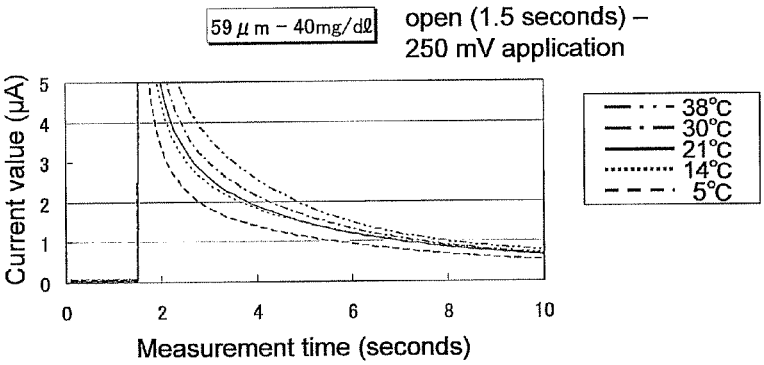


FIG. 23D

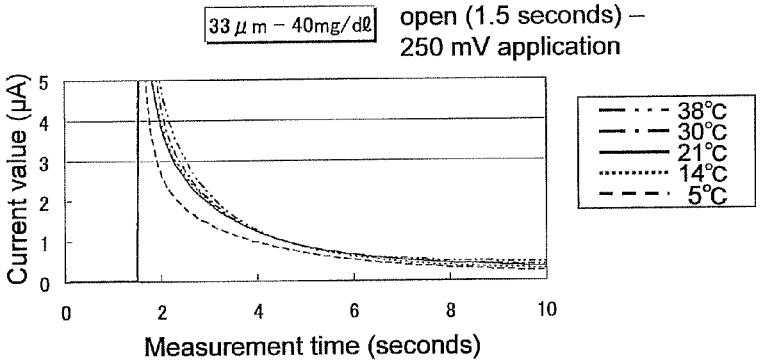


FIG. 24A

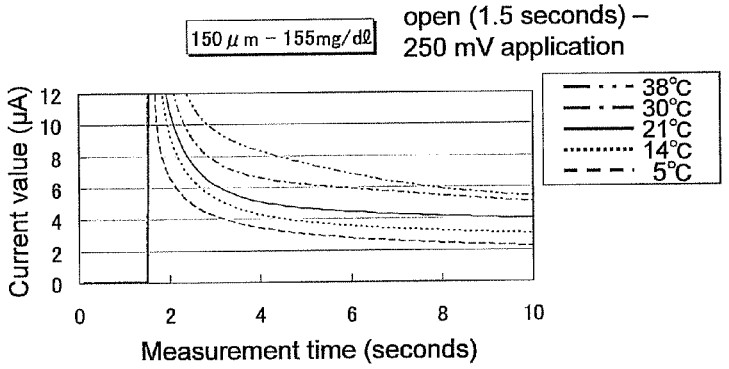


FIG. 24B

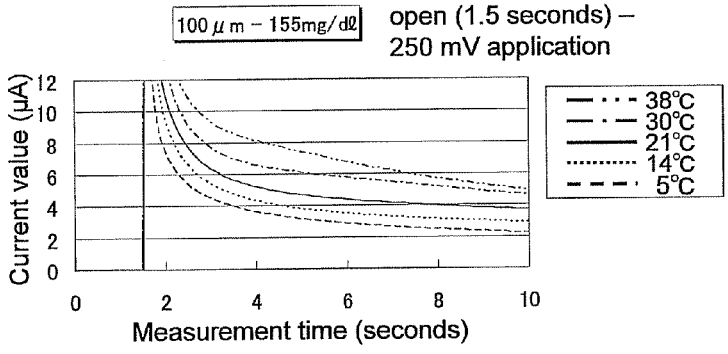


FIG. 24C

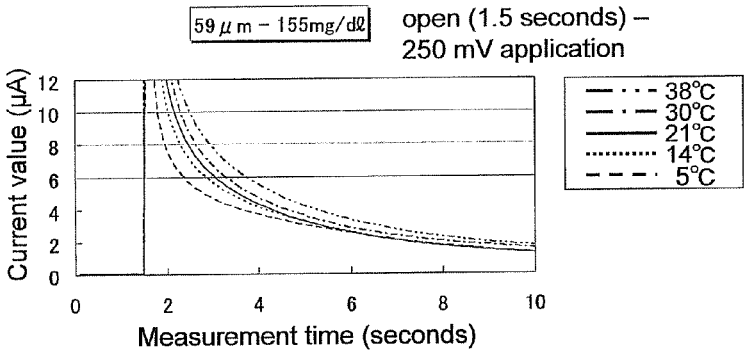


FIG. 24D

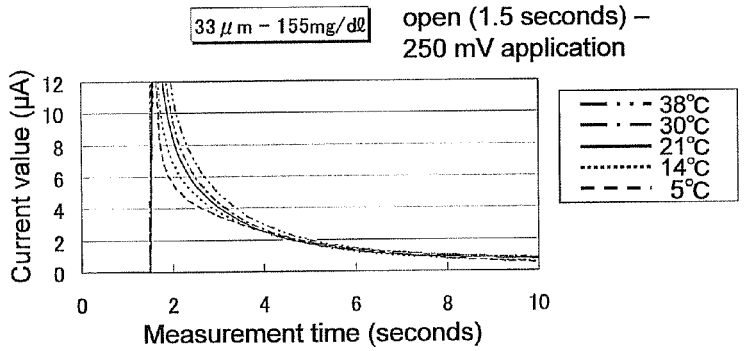


FIG. 25A

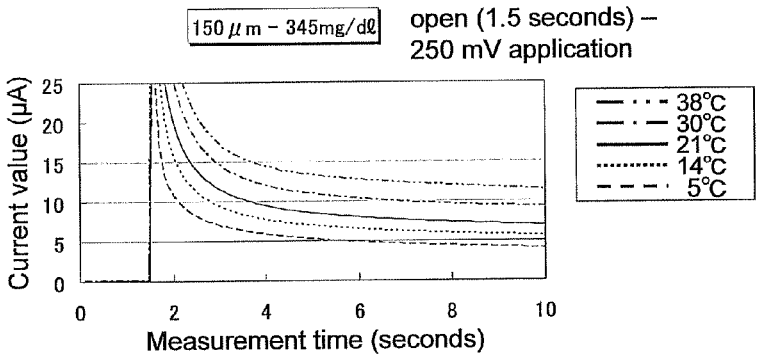


FIG. 25B

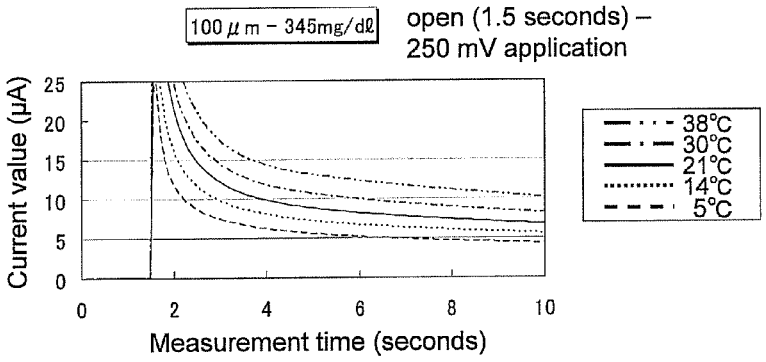


FIG. 25C

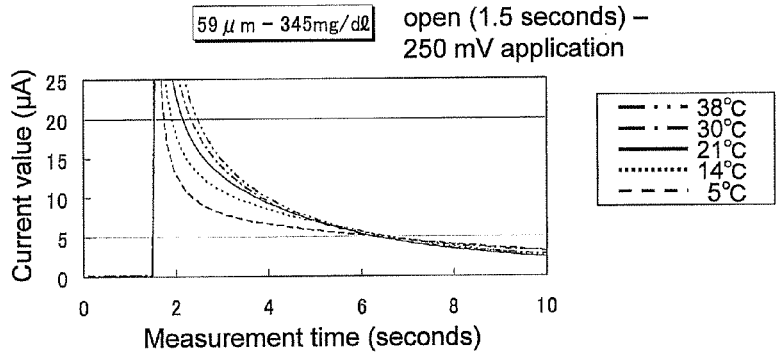


FIG. 25D

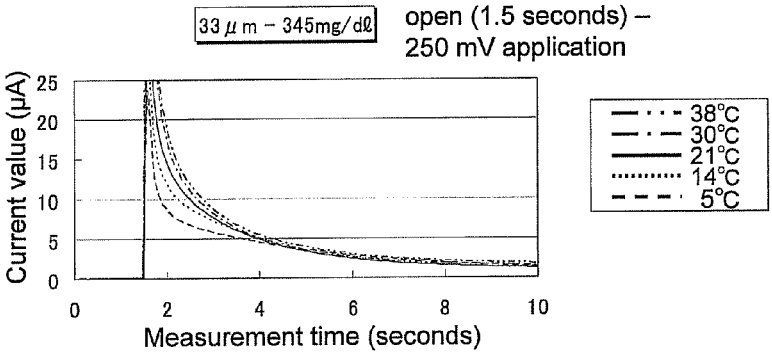


FIG. 26A

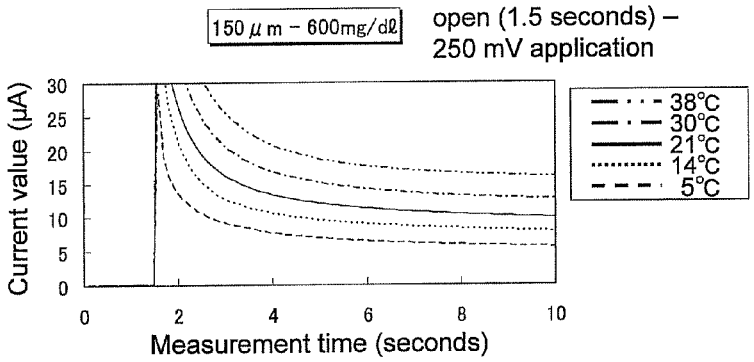


FIG. 26B

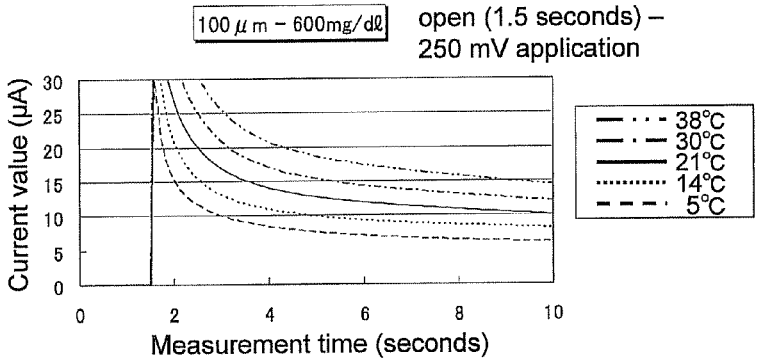


FIG. 26C

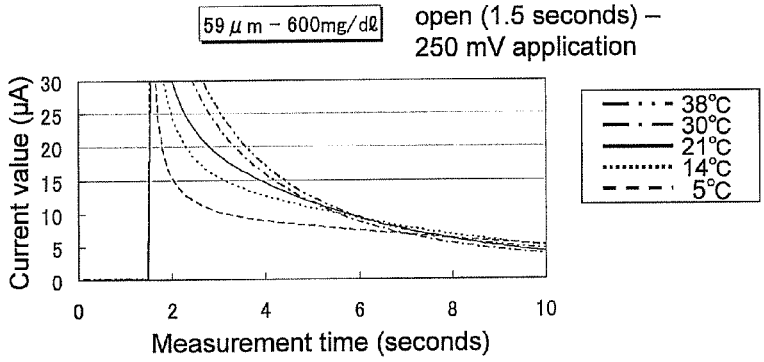


FIG. 26D

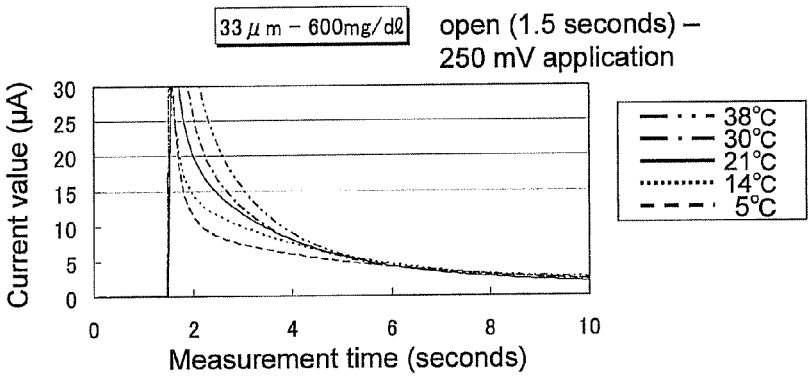


FIG. 27A

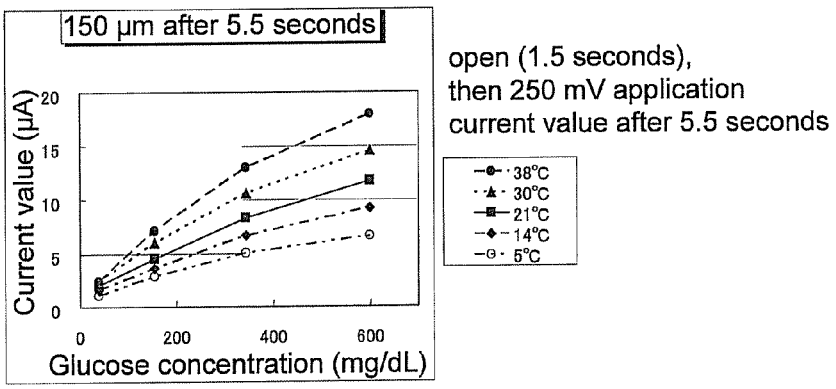


FIG. 27B

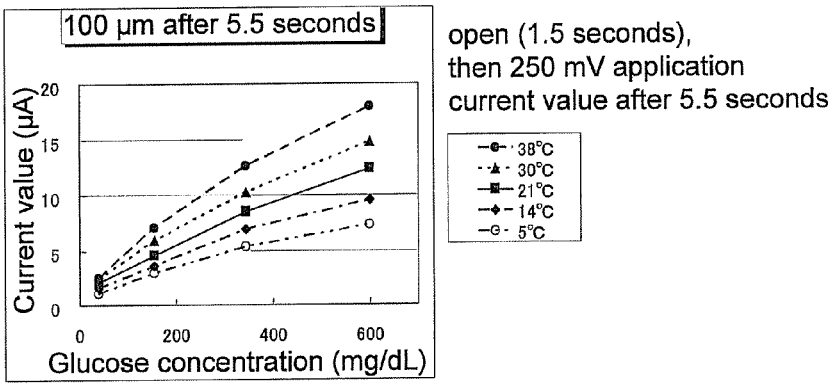


FIG. 27C

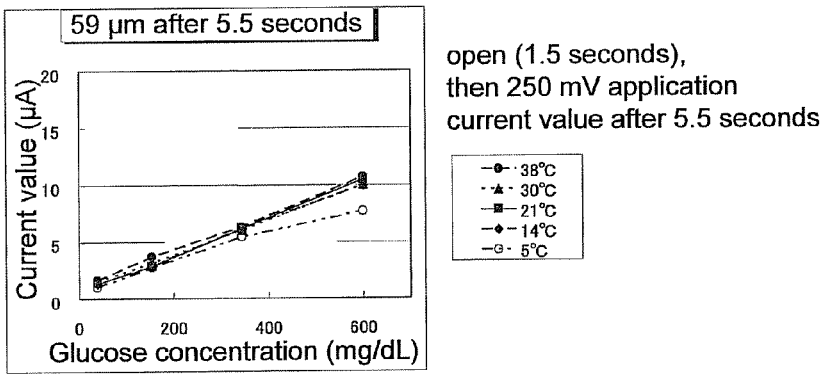


FIG. 27D

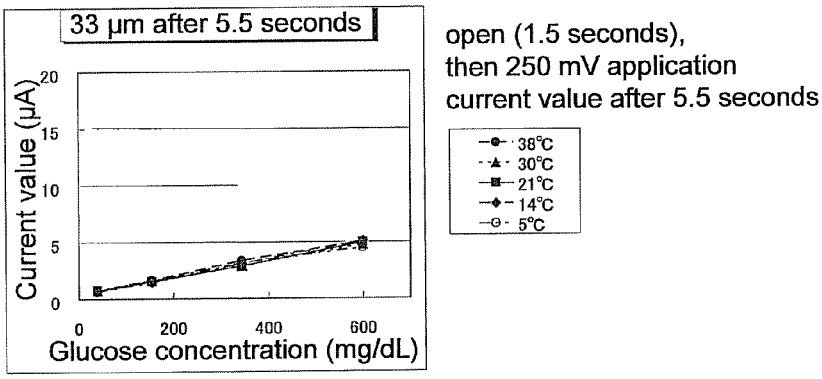


FIG. 28A

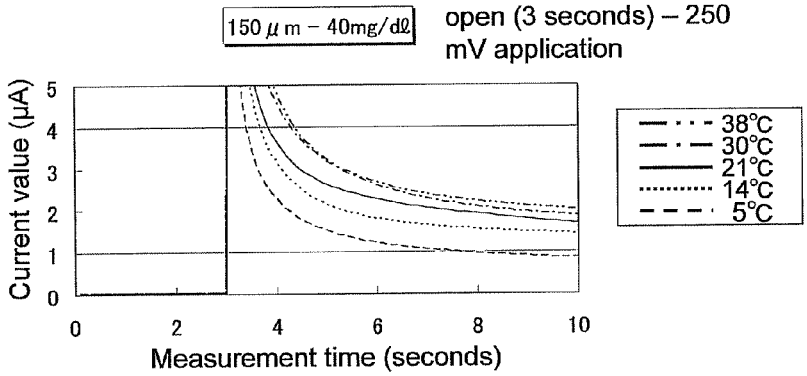


FIG. 28B

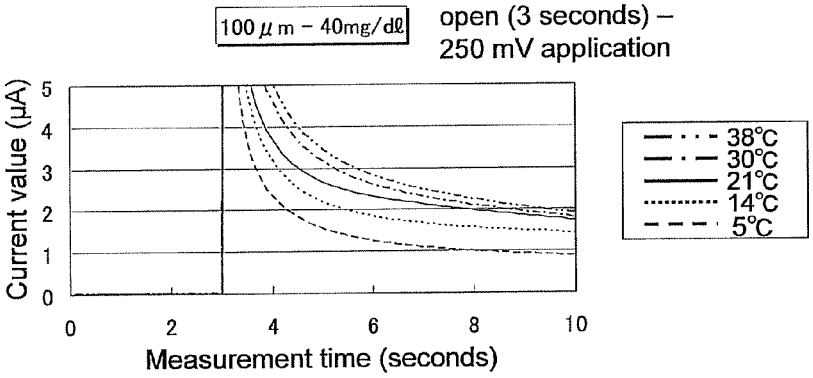


FIG. 28C

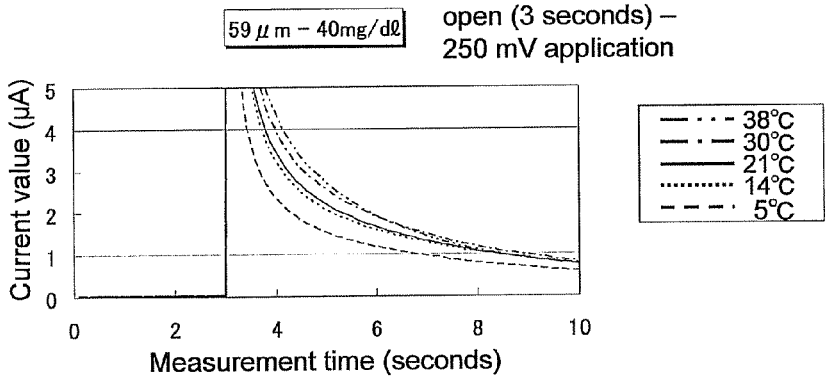


FIG. 28D

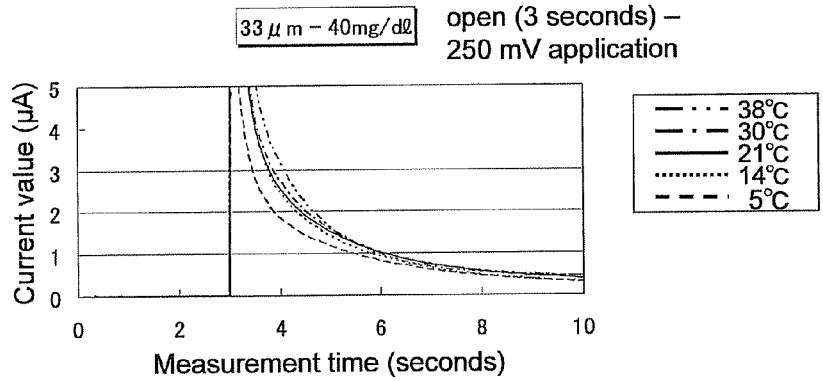


FIG. 29A

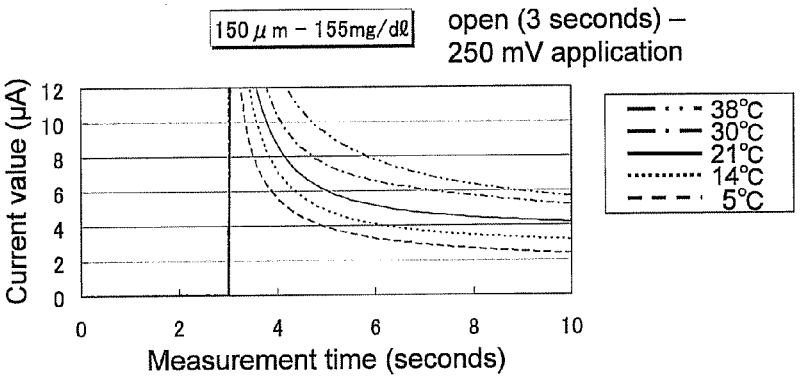


FIG. 29B

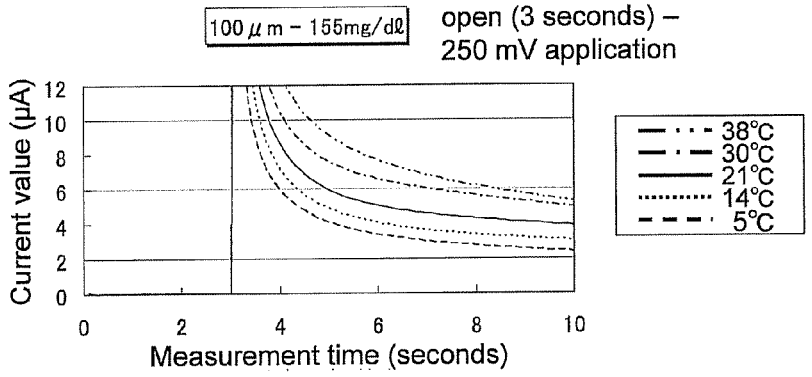


FIG. 29C

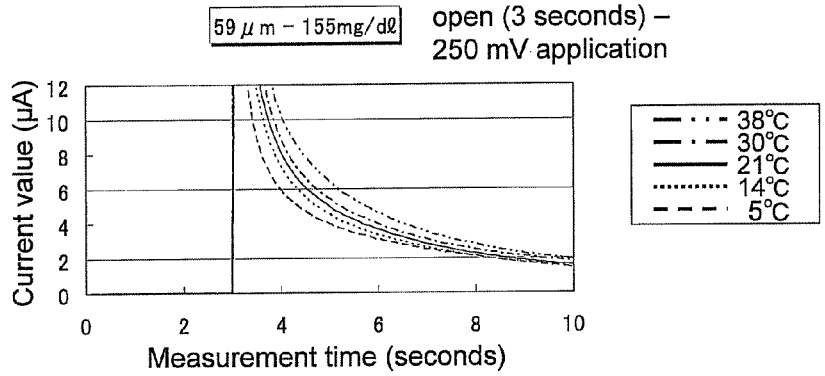


FIG. 29D

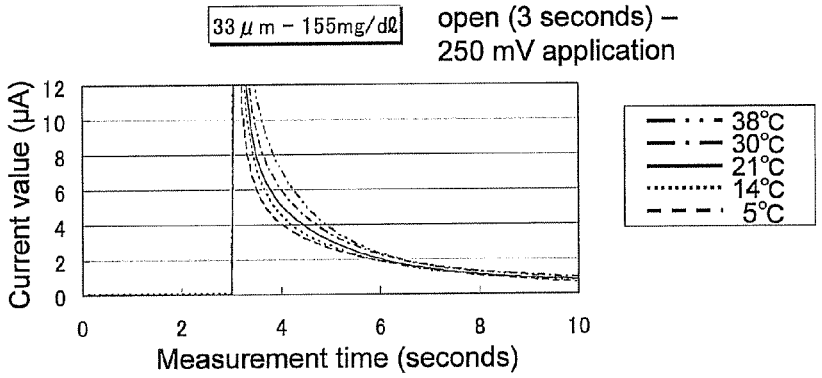


FIG. 30A

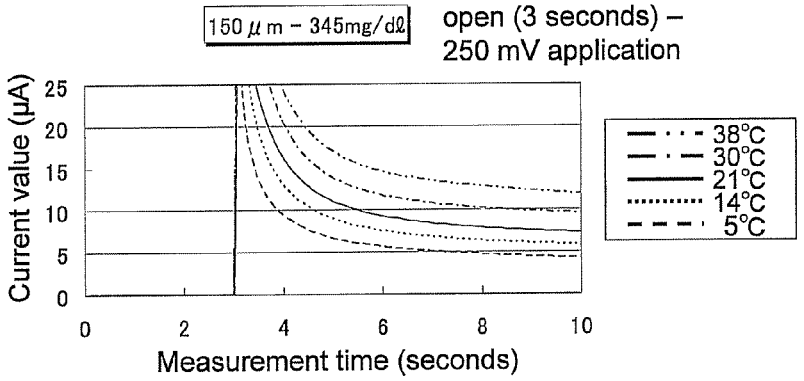


FIG. 30B

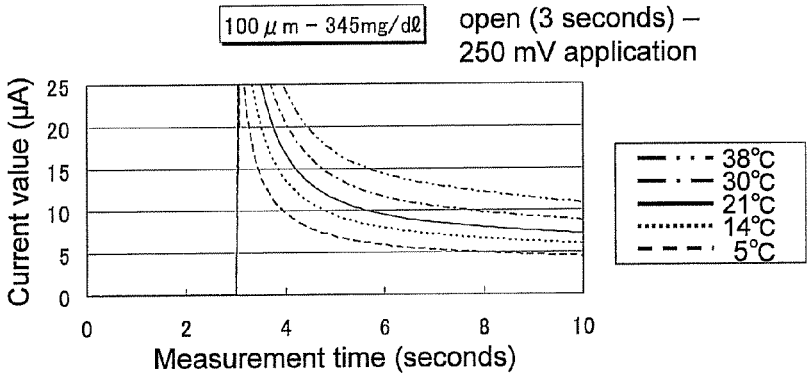


FIG. 30C

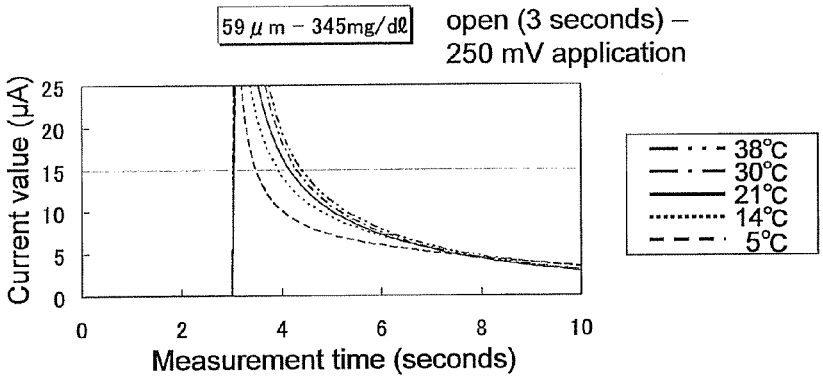


FIG. 30D

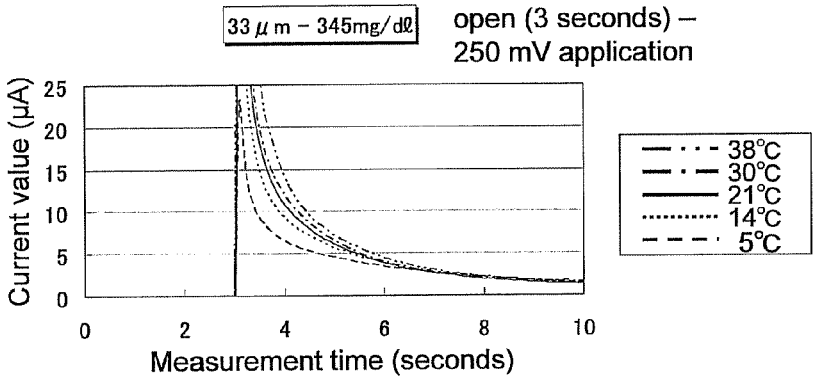


FIG. 31A

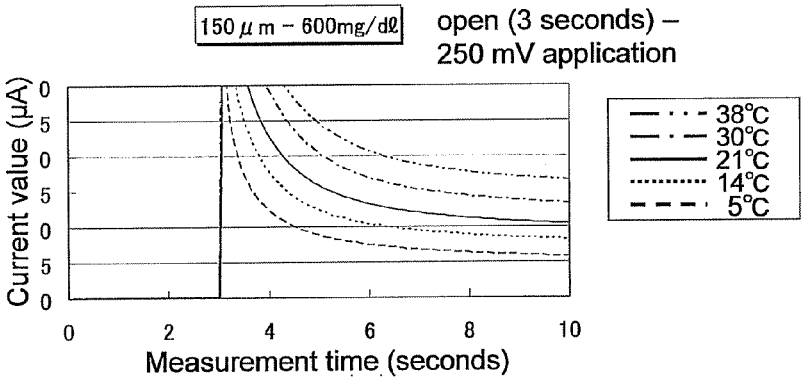


FIG. 31B

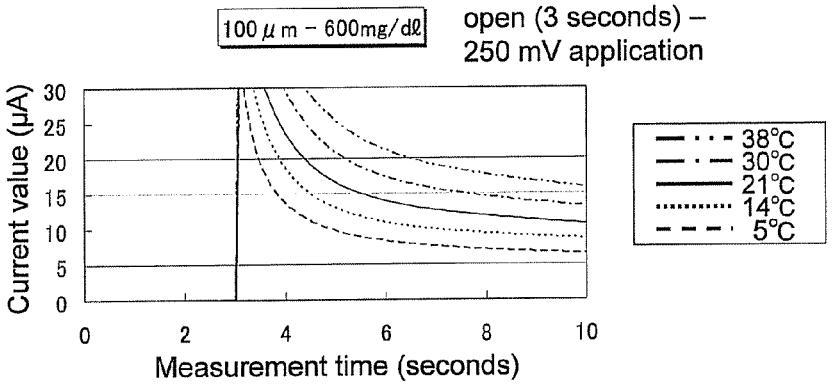


FIG. 31C

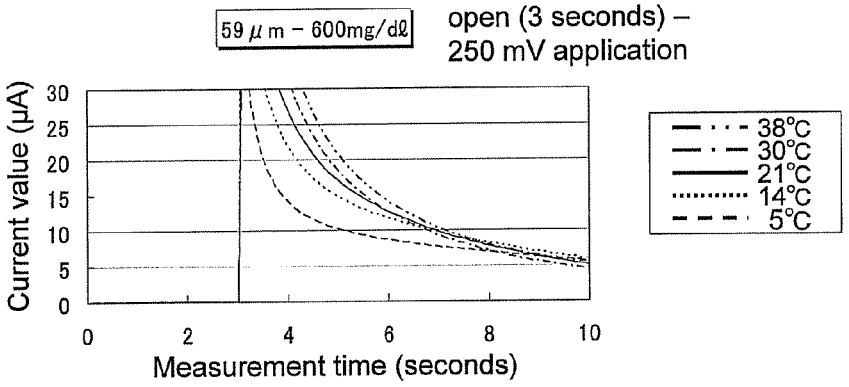


FIG. 31D

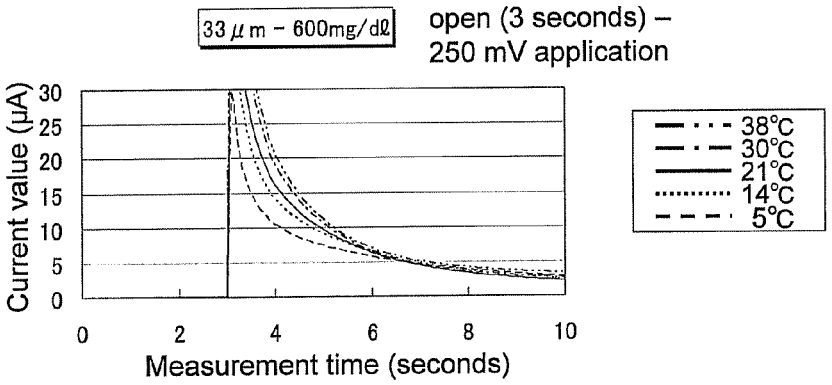


FIG. 32A

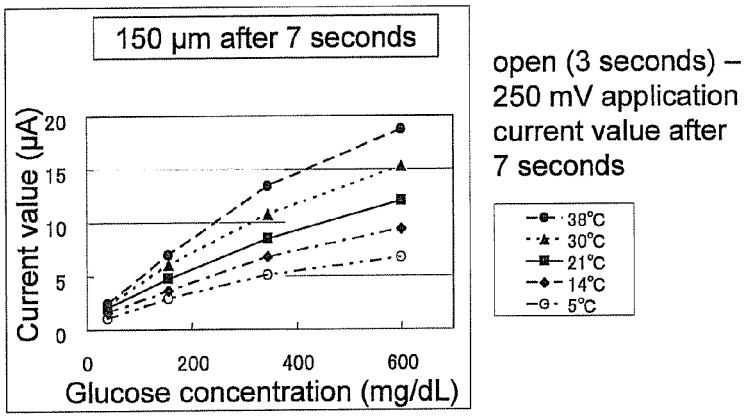


FIG. 32B

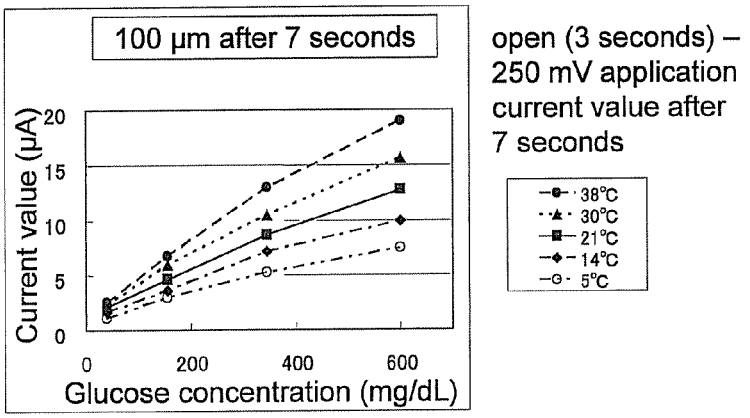


FIG. 32C

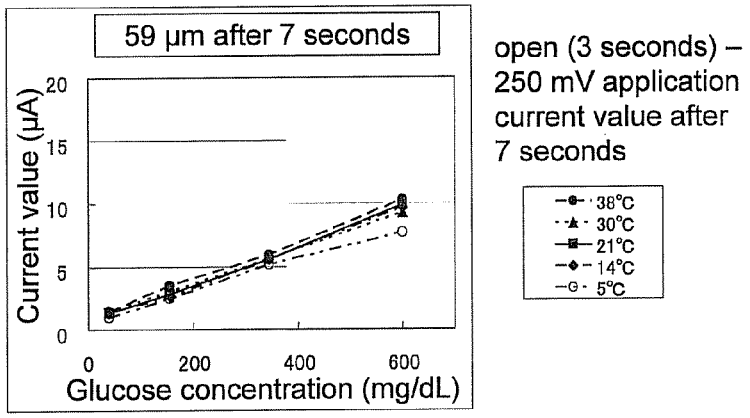


FIG. 32D

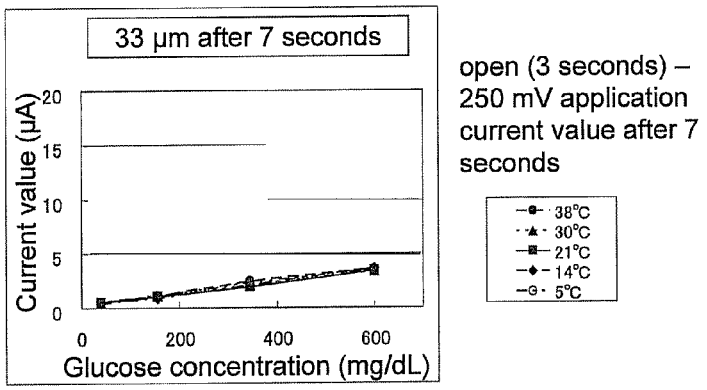


FIG. 33A

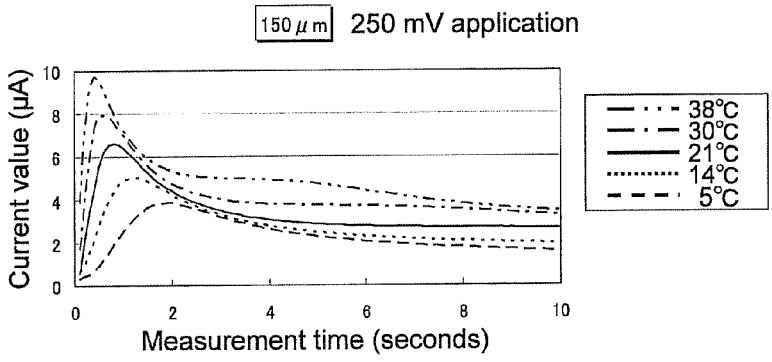


FIG. 33B

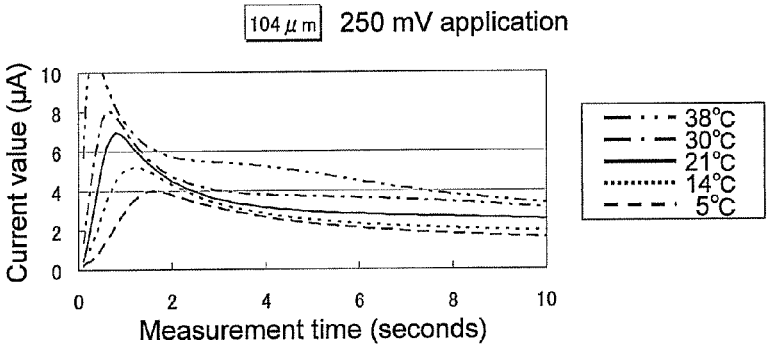


FIG. 33C

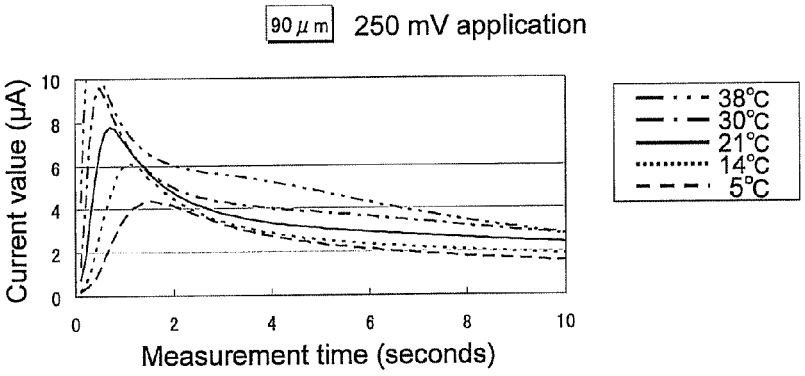


FIG. 33D

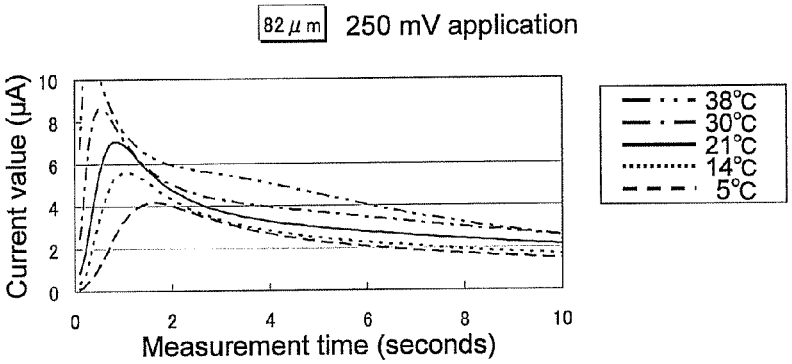


FIG. 34A

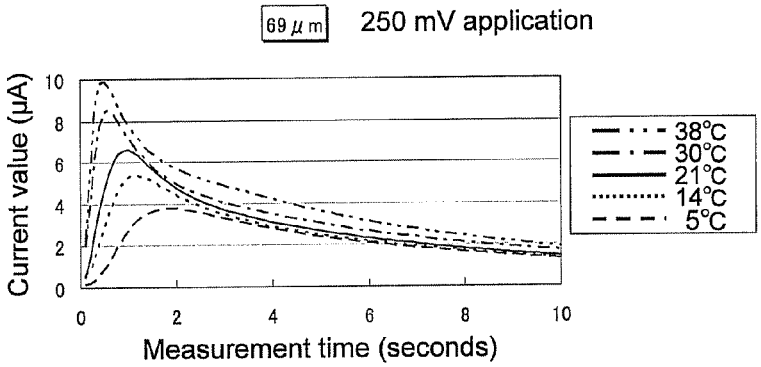


FIG. 34B

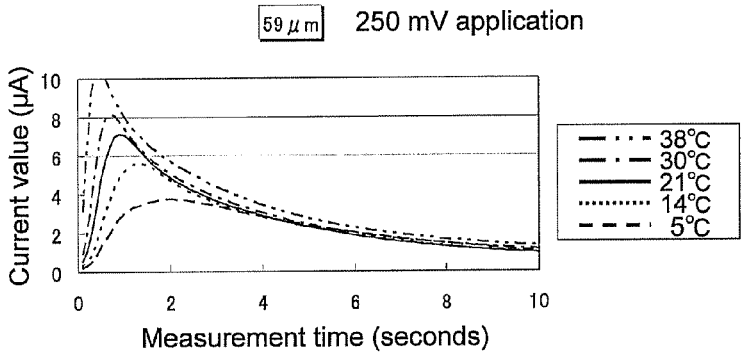


FIG. 34C

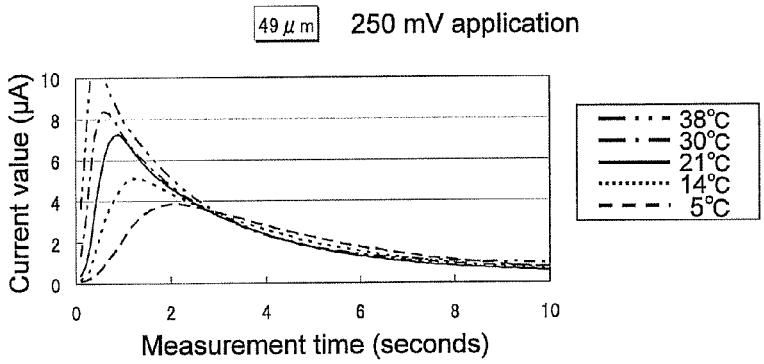


FIG. 34D

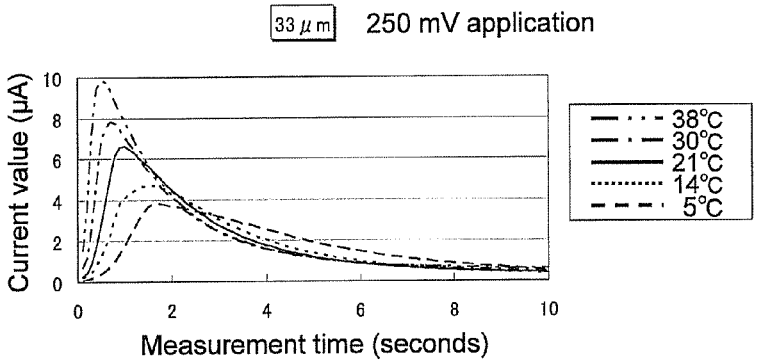


FIG. 35A

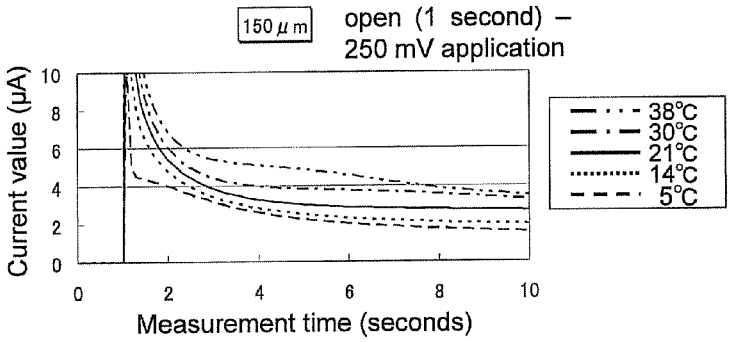


FIG. 35B

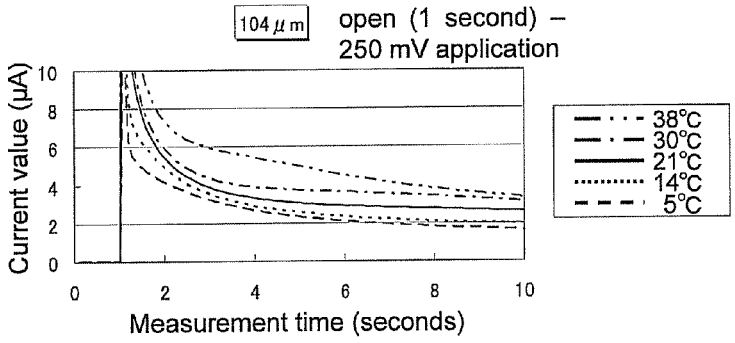


FIG. 35C

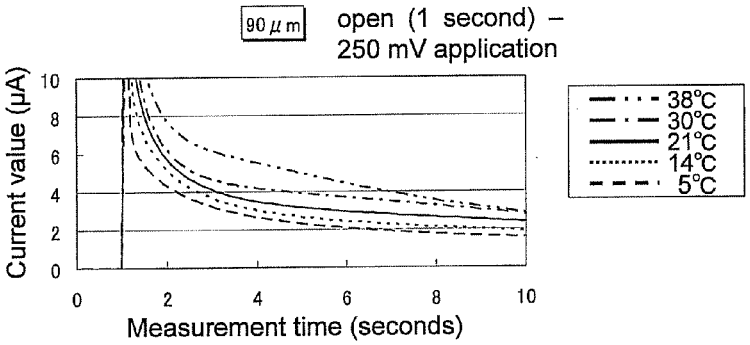


FIG. 35D

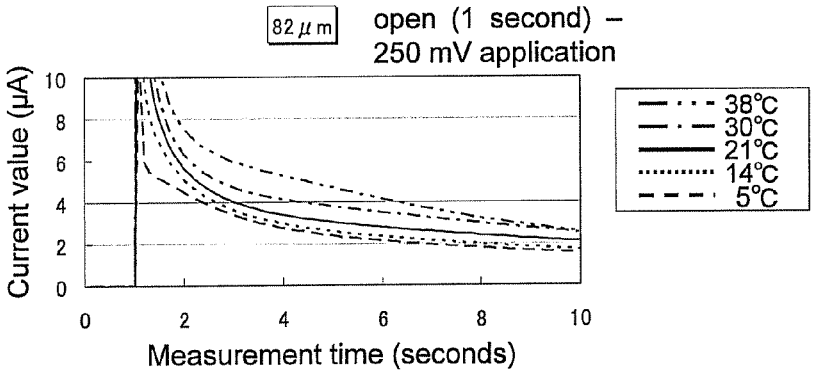


FIG. 36A

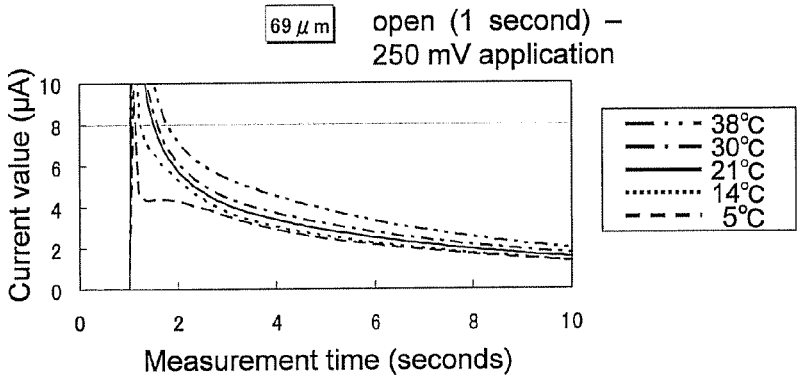


FIG. 36B

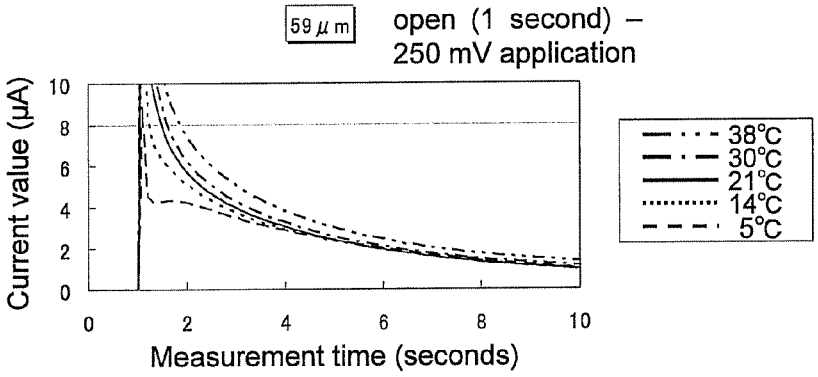


FIG. 36C

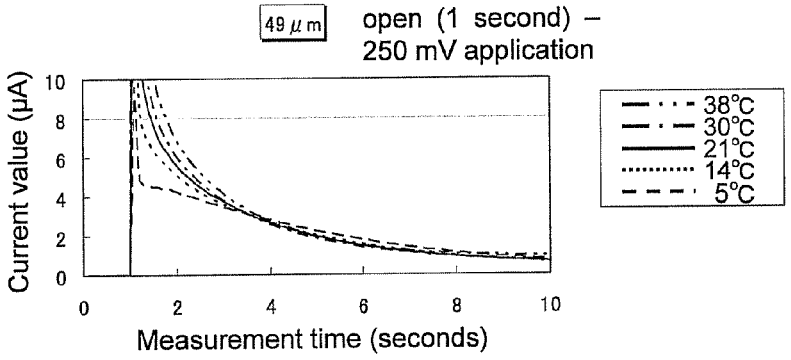


FIG. 36D

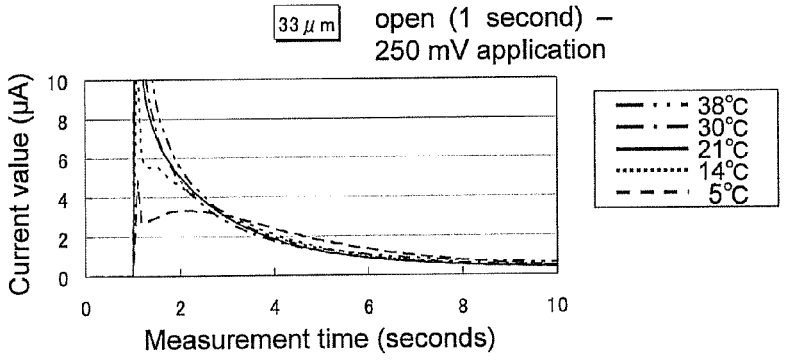


FIG. 37A

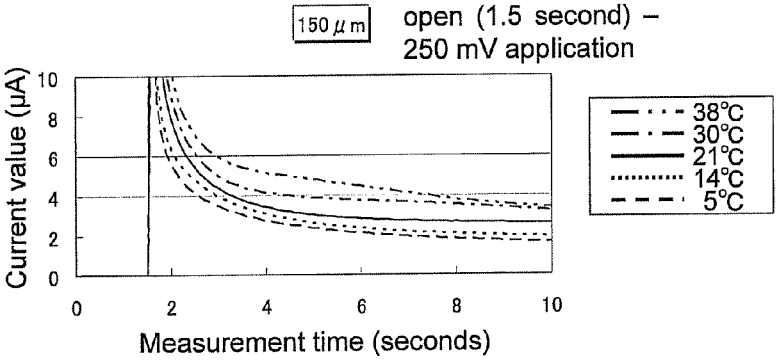


FIG. 37B

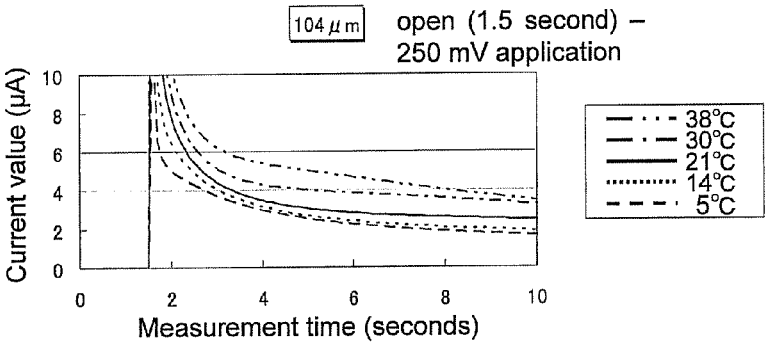


FIG. 37C

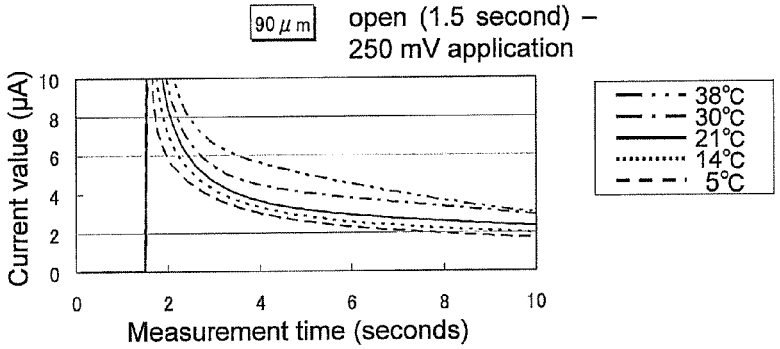


FIG. 37D

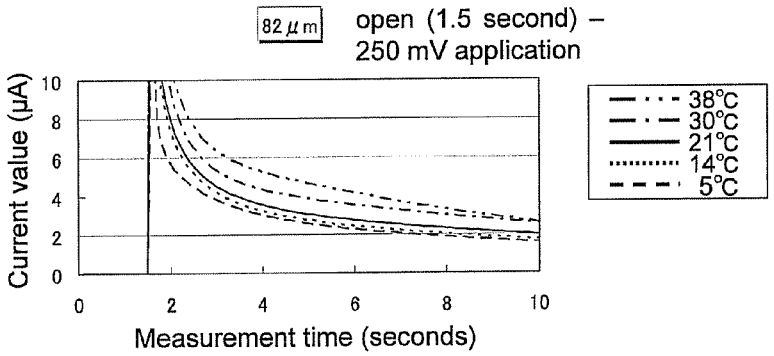


FIG. 38A

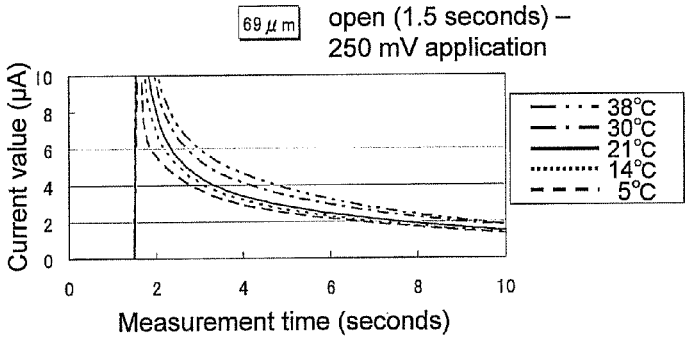


FIG. 38B

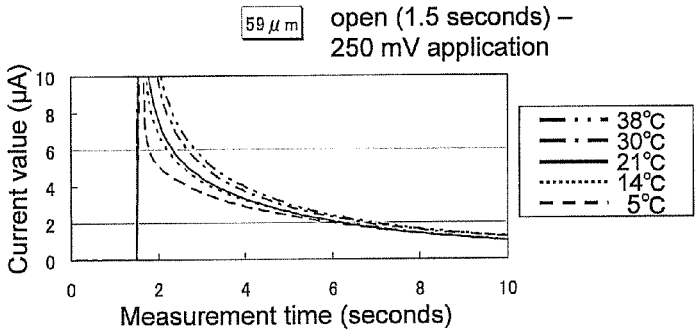


FIG. 38C

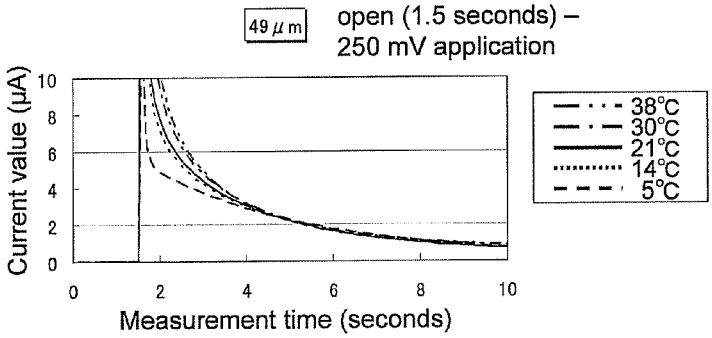


FIG. 38D

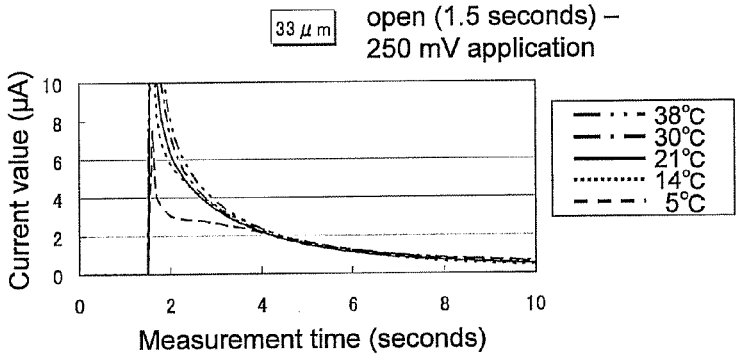


FIG. 39A

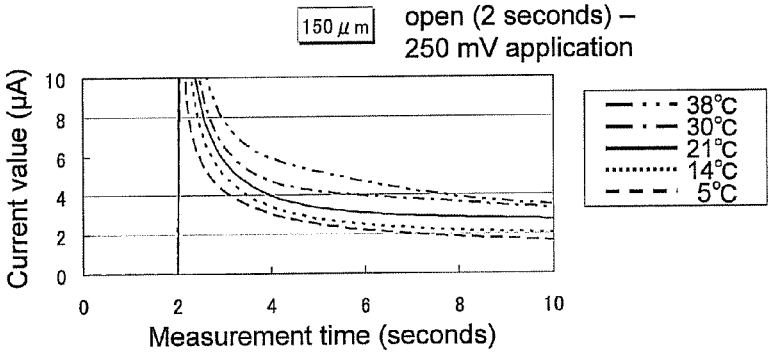


FIG. 39B

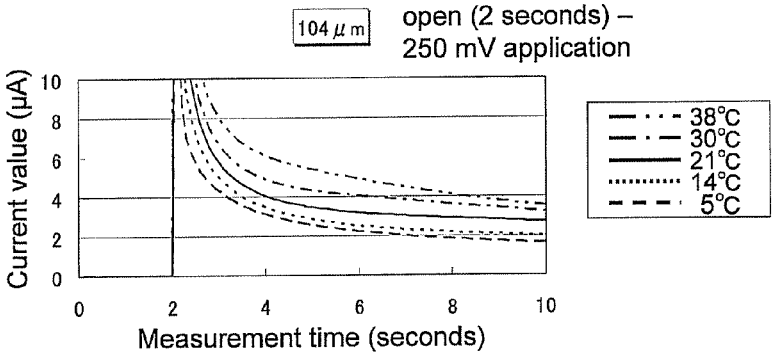


FIG. 39C

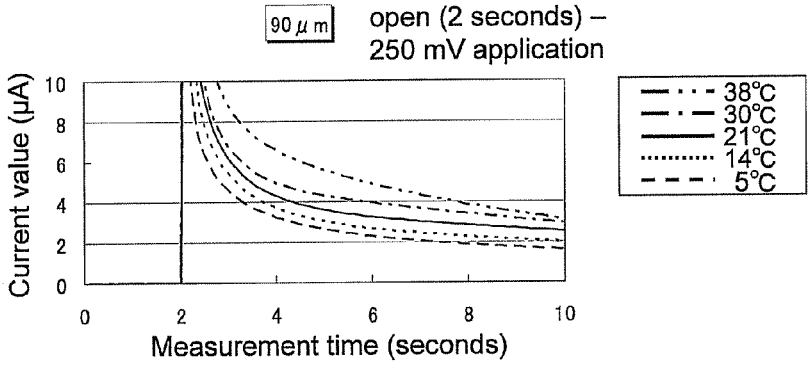


FIG. 39D

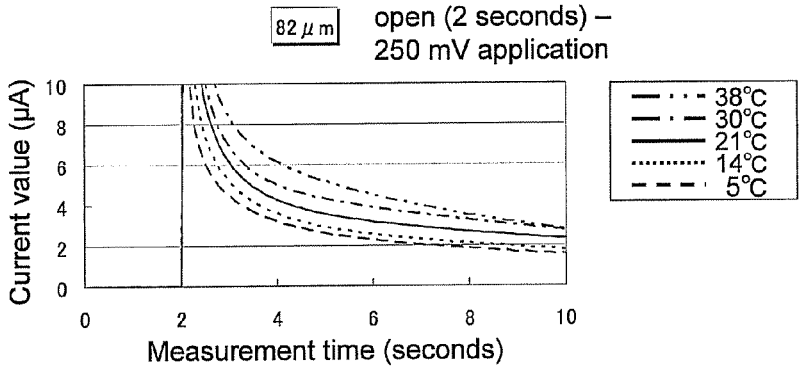


FIG. 40A

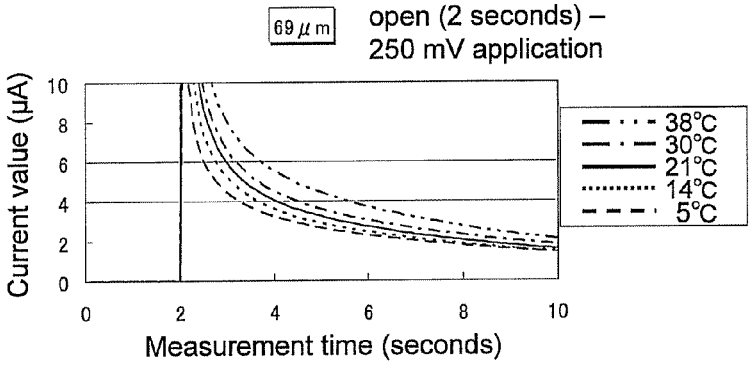


FIG. 40B

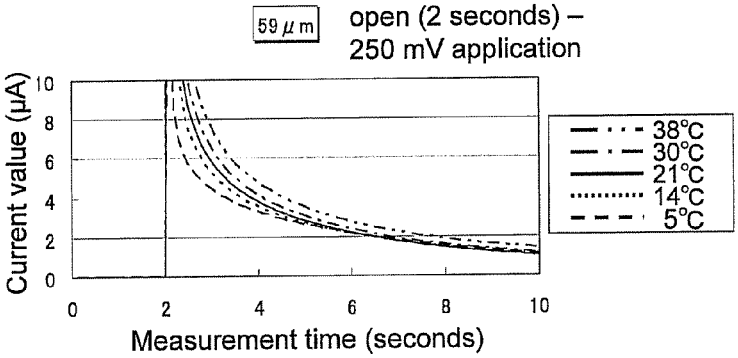


FIG. 40C

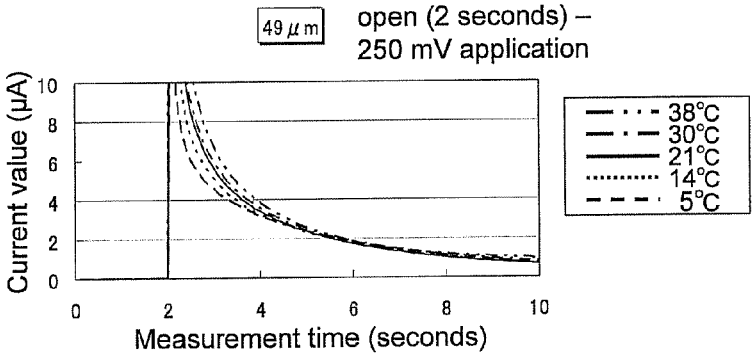


FIG. 40D

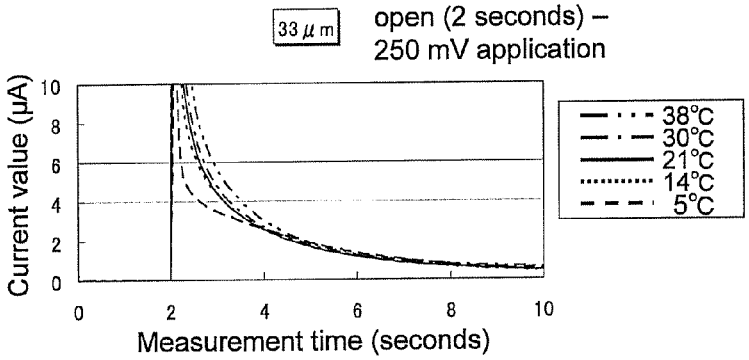


FIG. 41A

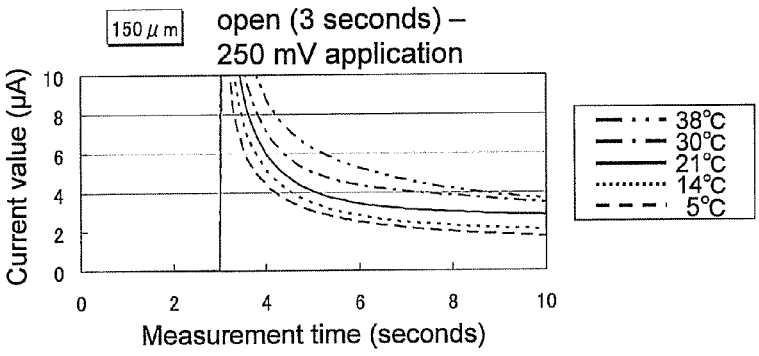


FIG. 41B

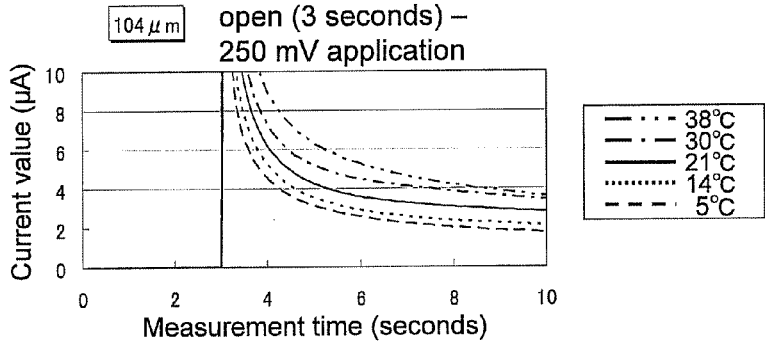


FIG. 41C

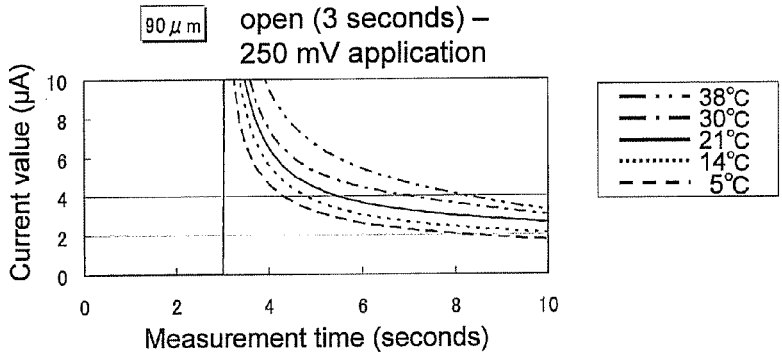


FIG. 41D

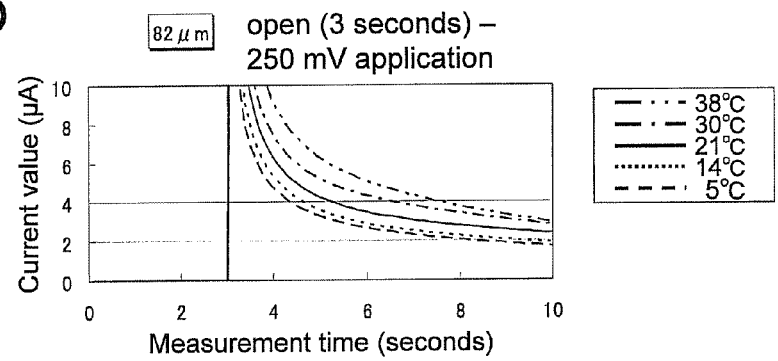


FIG. 42A

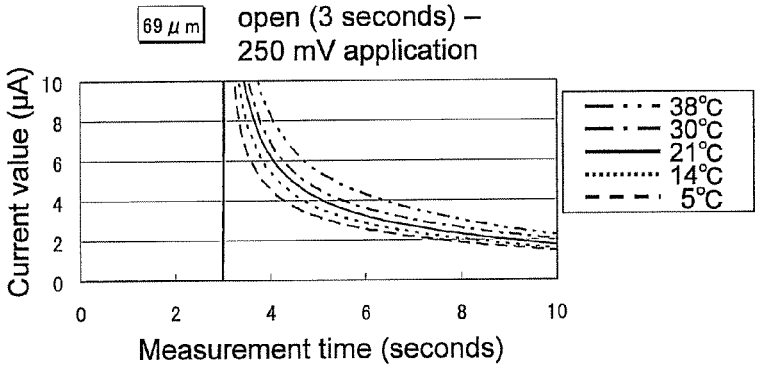


FIG. 42B

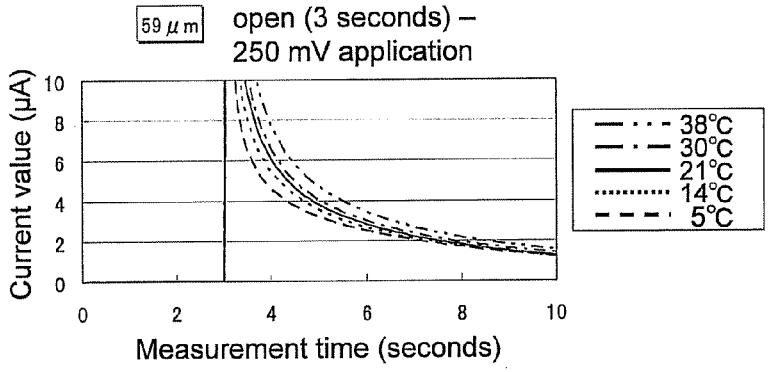


FIG. 42C

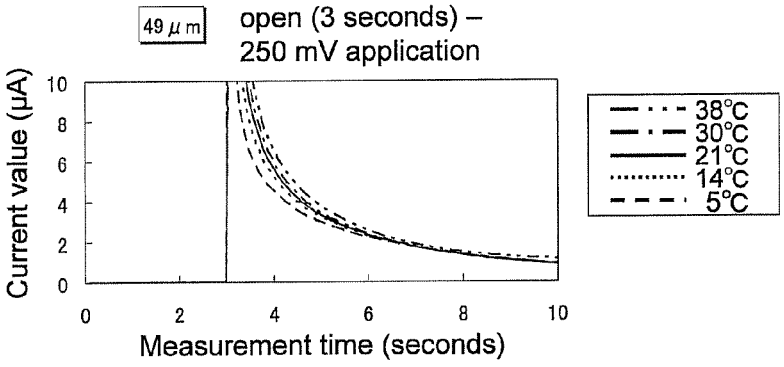


FIG. 42D

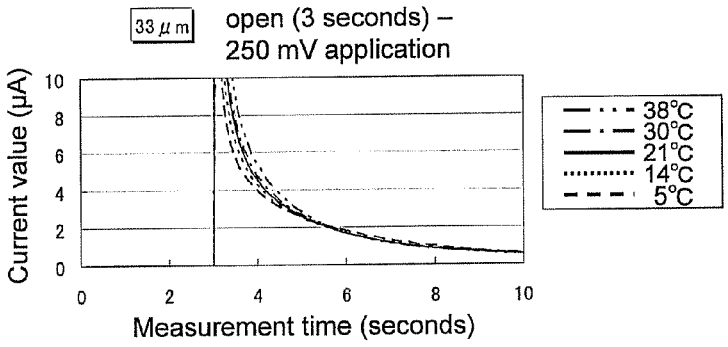


FIG. 43A

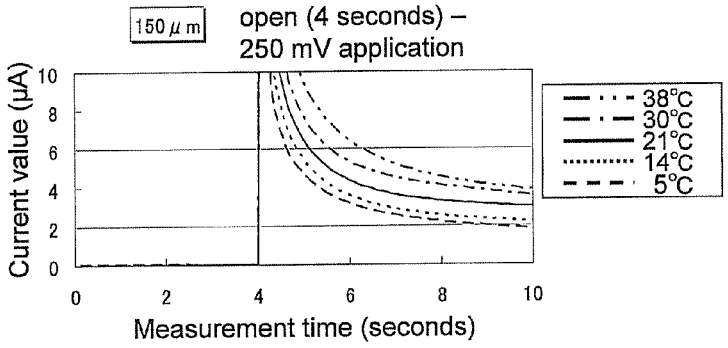


FIG. 43B

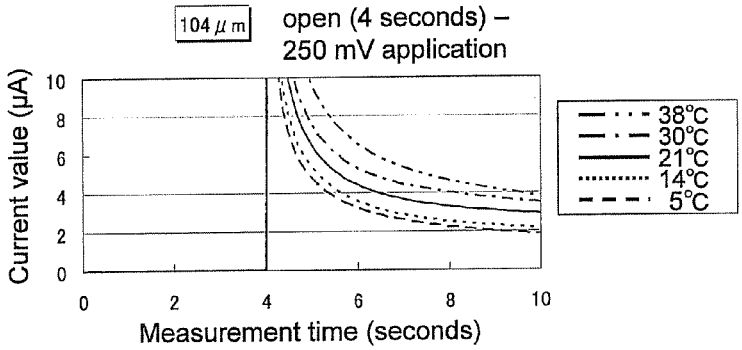


FIG. 43C

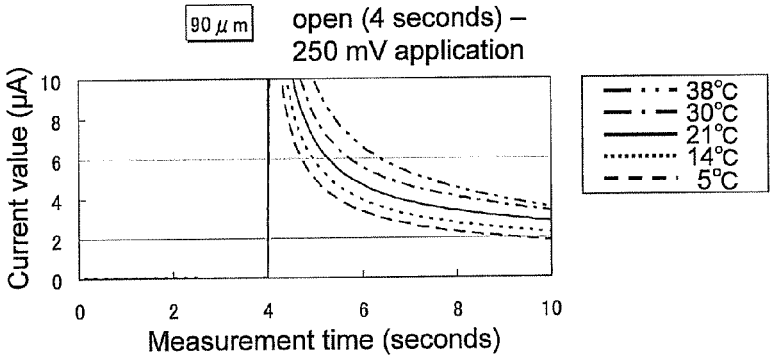


FIG. 43D

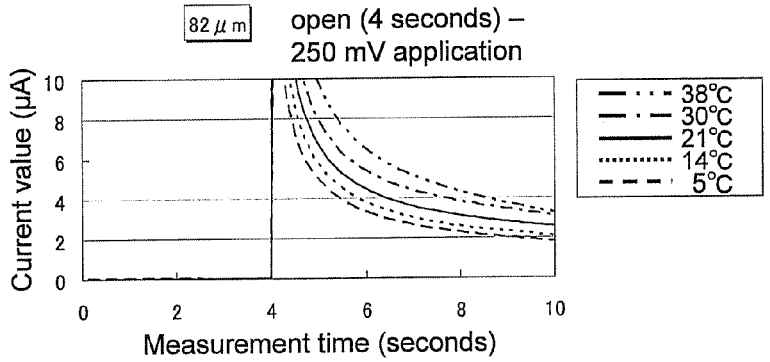


FIG. 44A

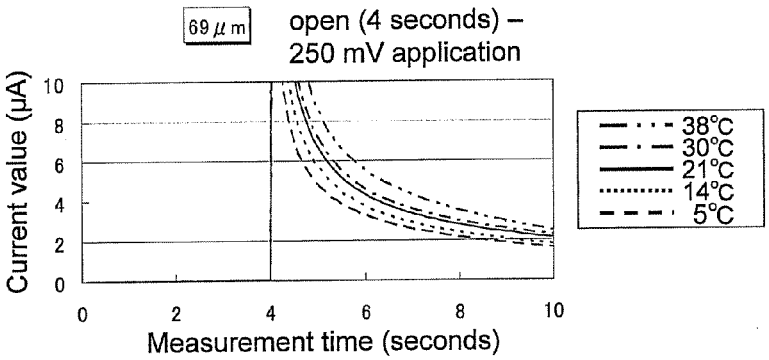


FIG. 44B

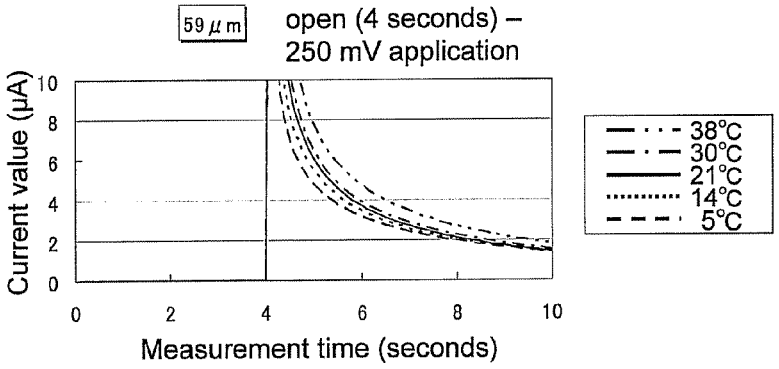


FIG. 44C

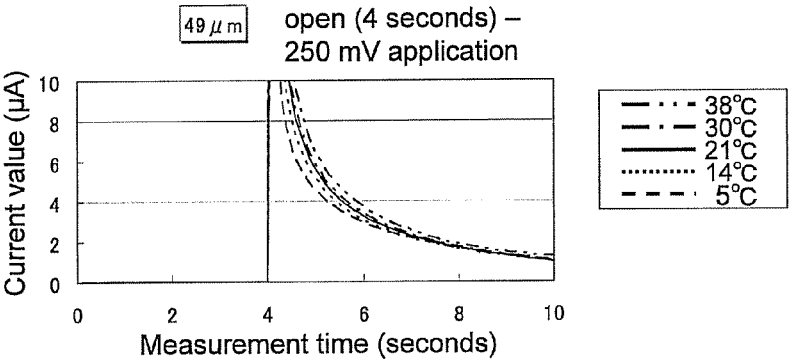


FIG. 44D

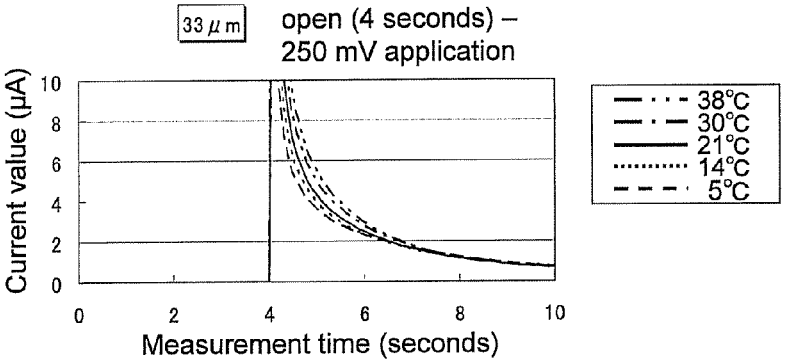


FIG. 45A

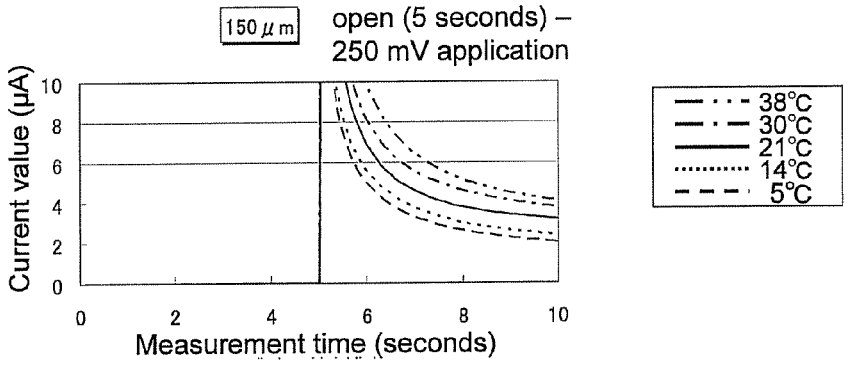


FIG. 45B

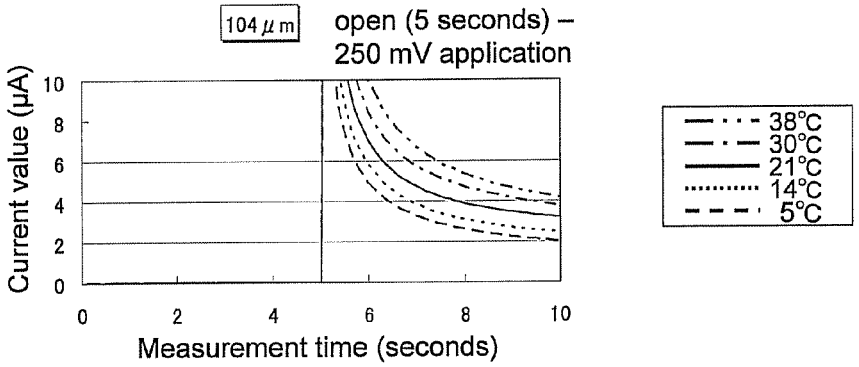


FIG. 45C

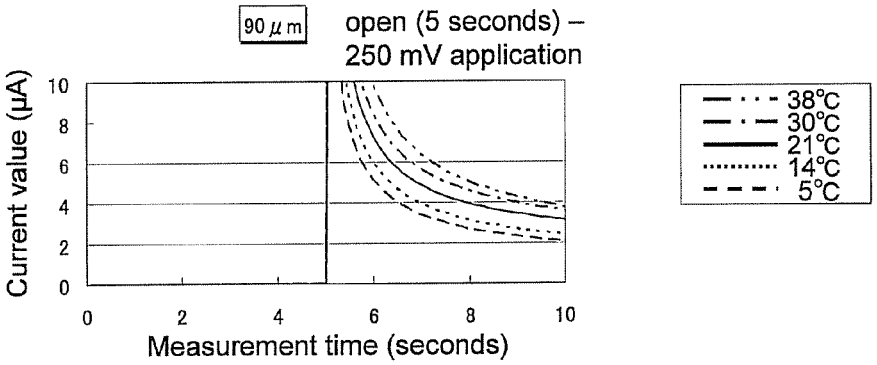


FIG. 45D

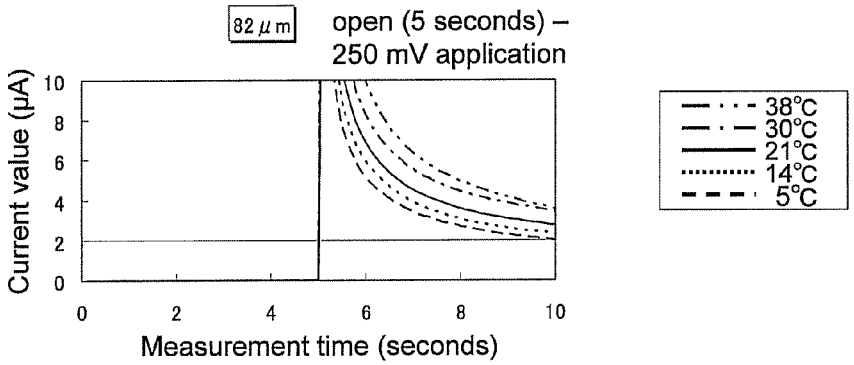


FIG. 46A

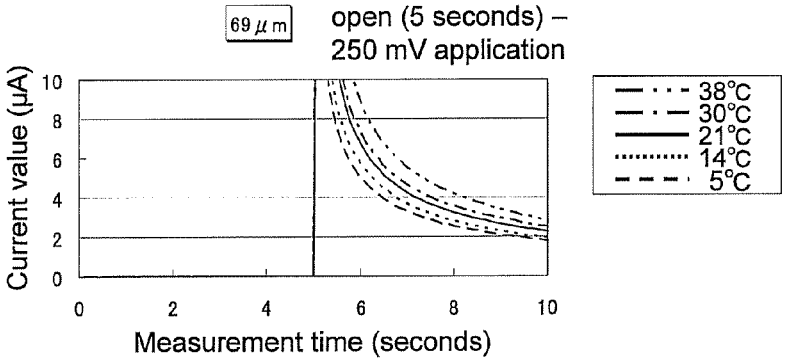


FIG. 46B

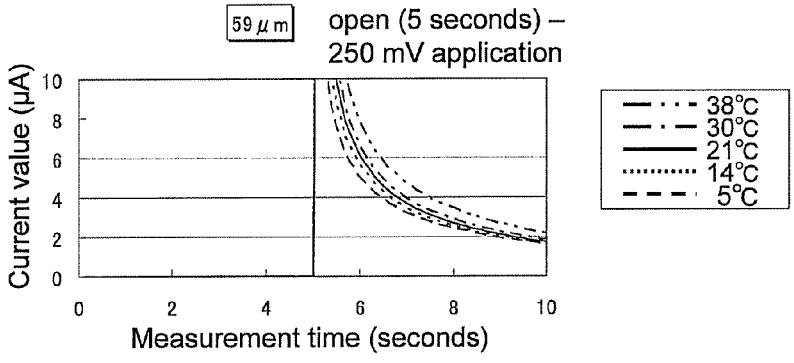


FIG. 46C

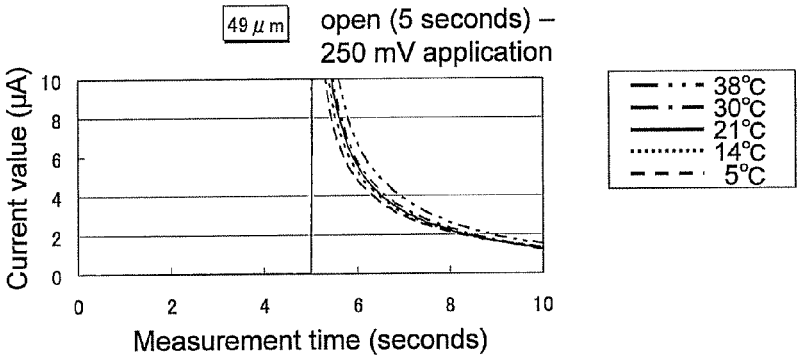


FIG. 46D

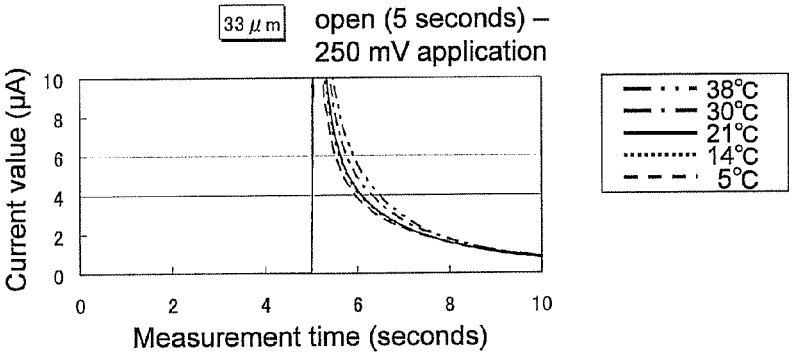


FIG. 47A

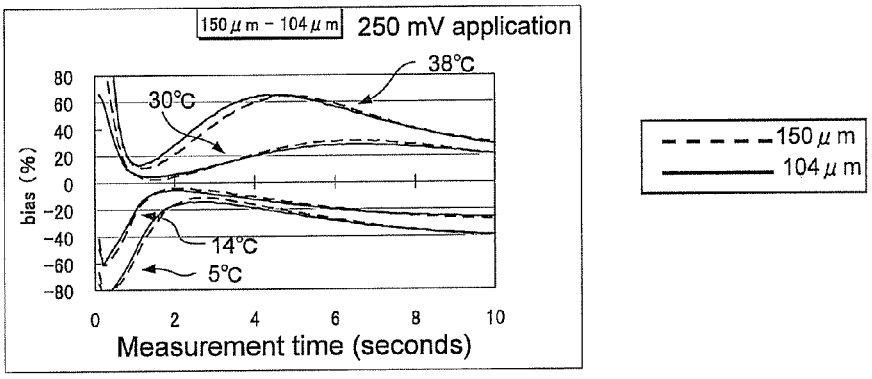


FIG. 47B

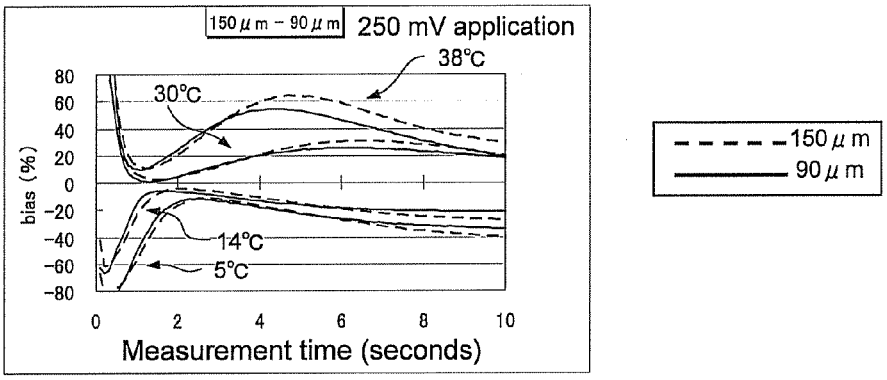


FIG. 47C

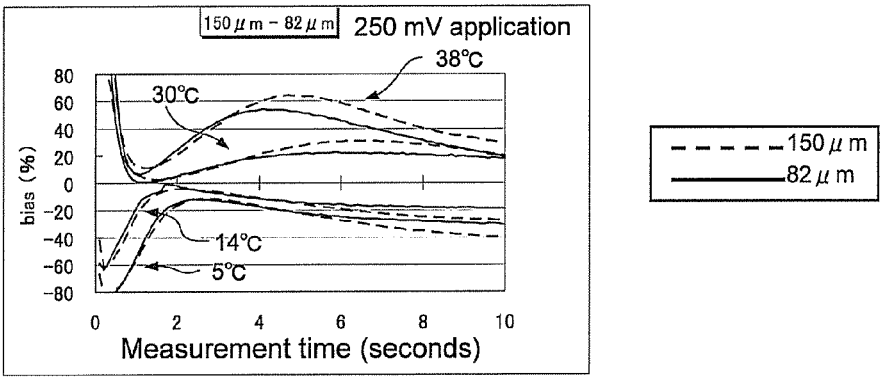


FIG. 47D

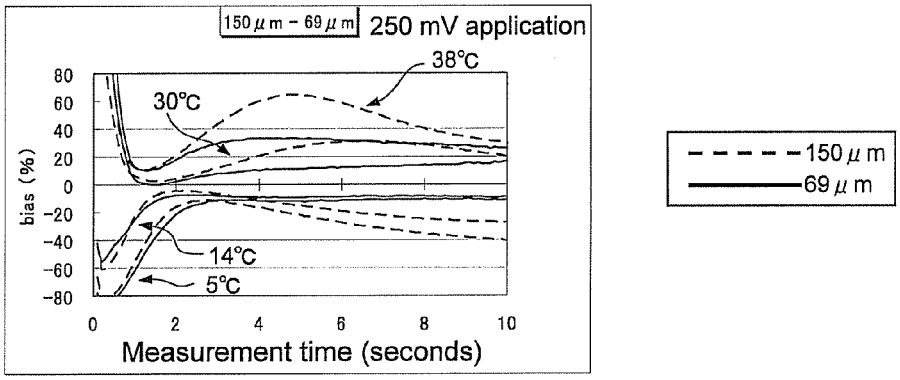


FIG. 48A

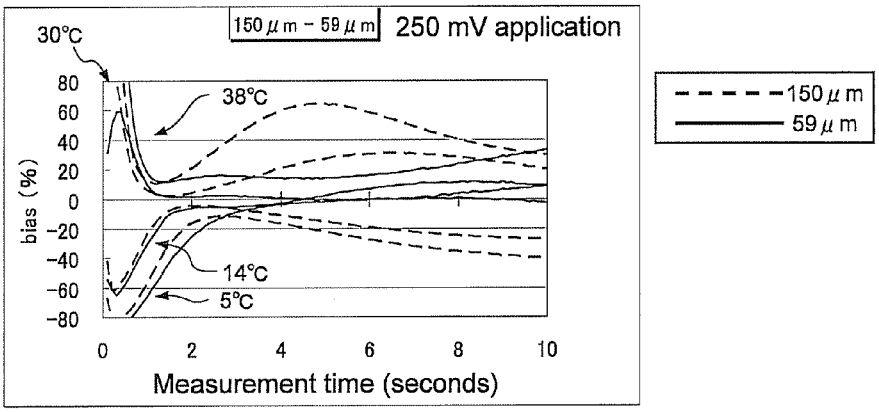


FIG. 48B

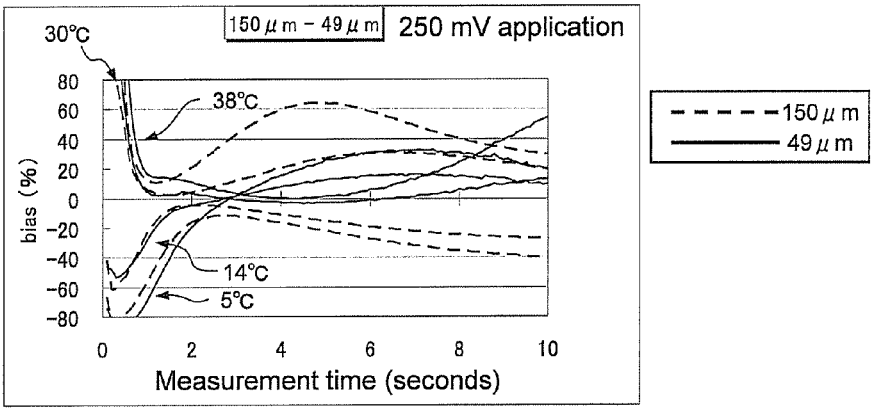


FIG. 48C

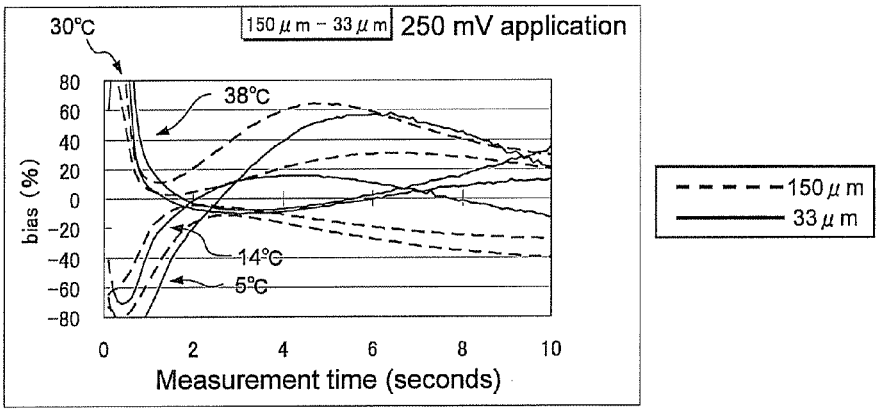


FIG. 49A

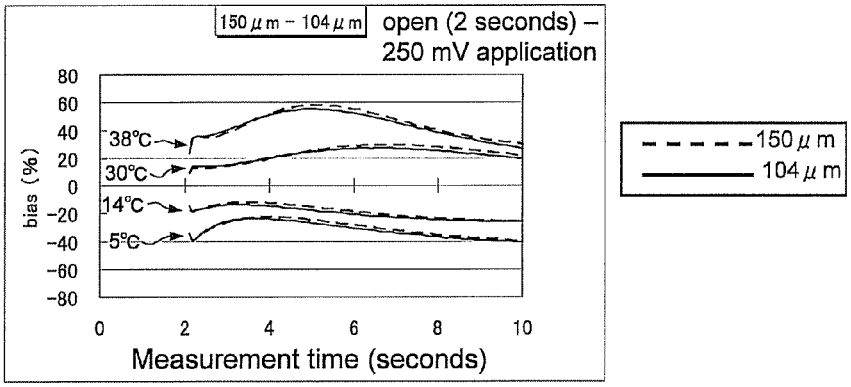


FIG. 49B

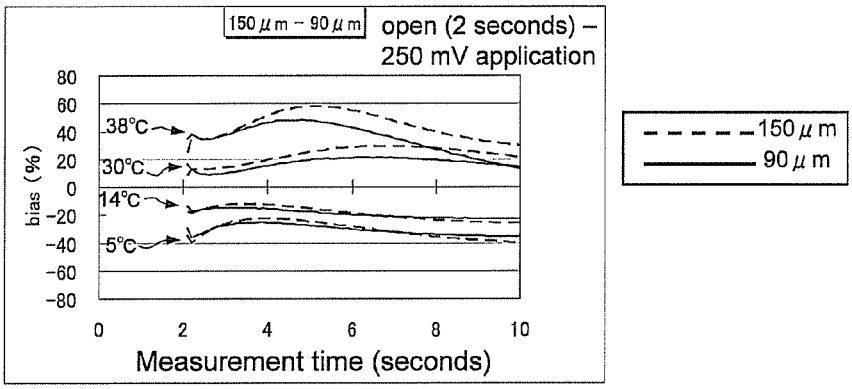


FIG. 49C

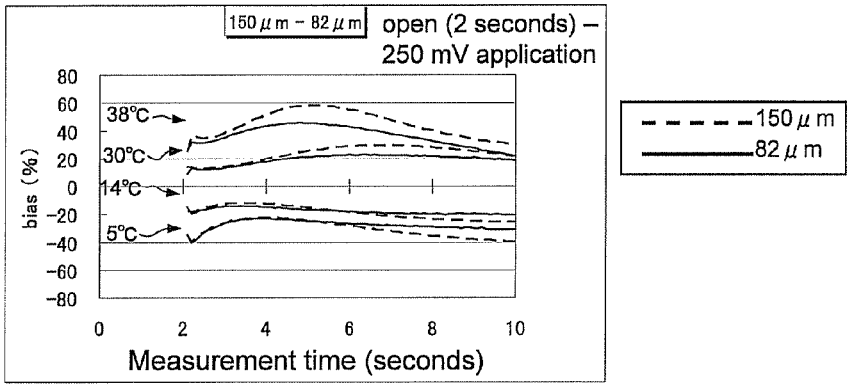


FIG. 49D

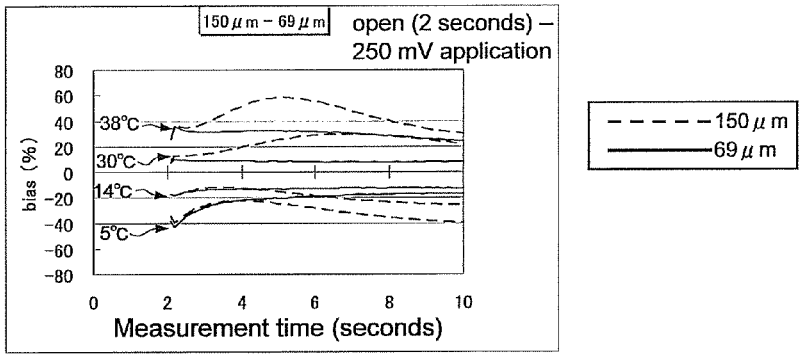


FIG. 50A

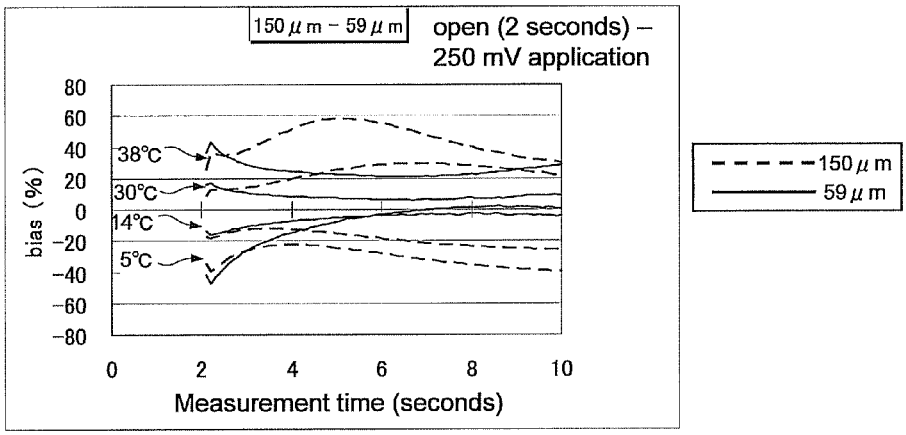


FIG. 50B

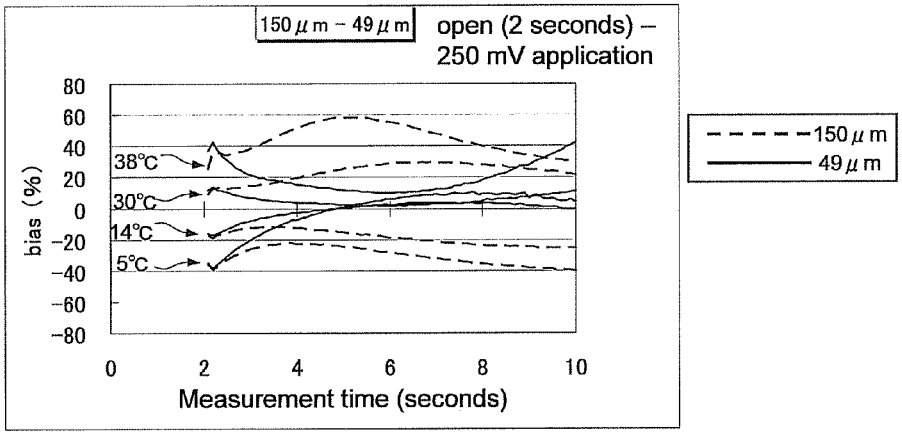


FIG. 50C

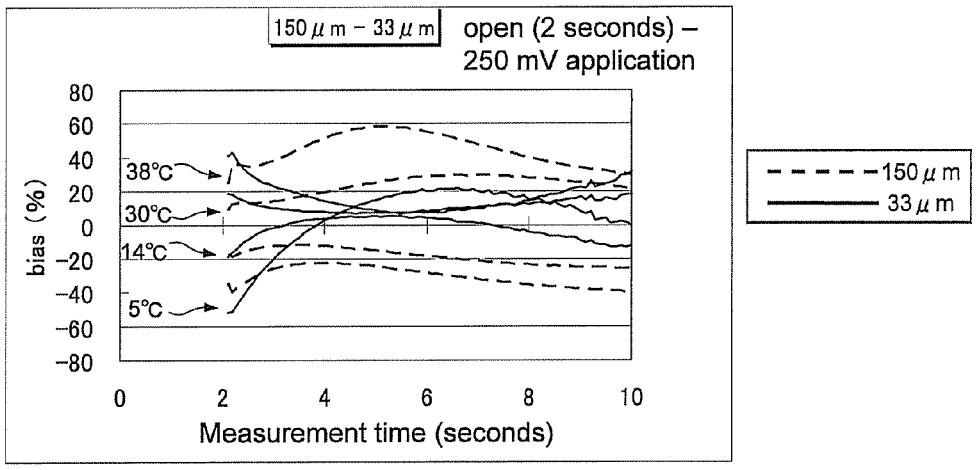


FIG. 51A

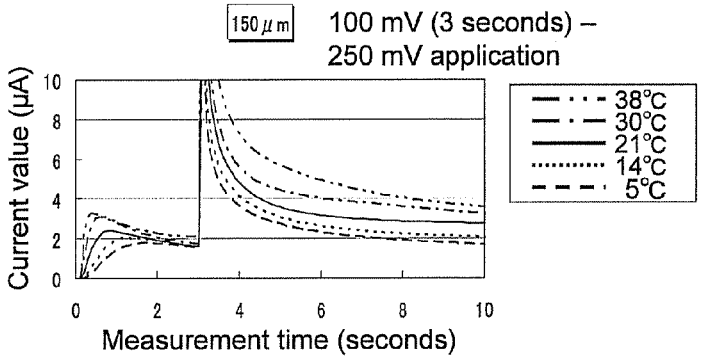


FIG. 51B

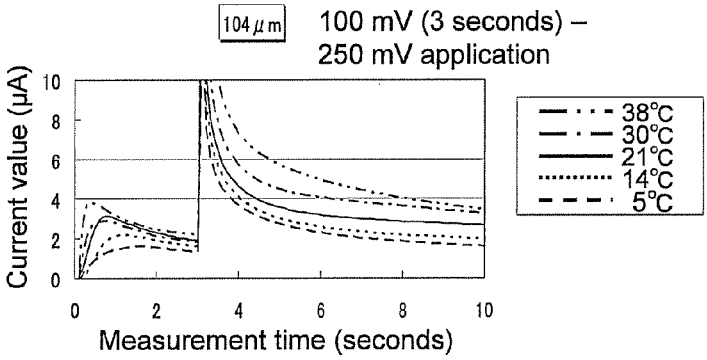


FIG. 51C

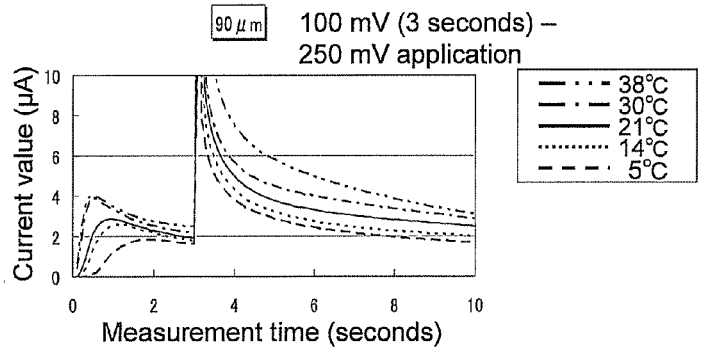


FIG. 51D

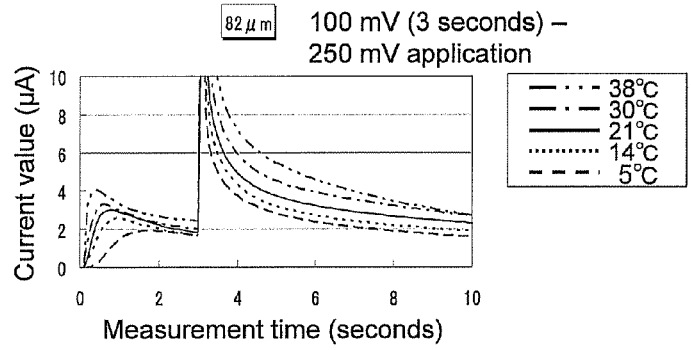


FIG. 52A

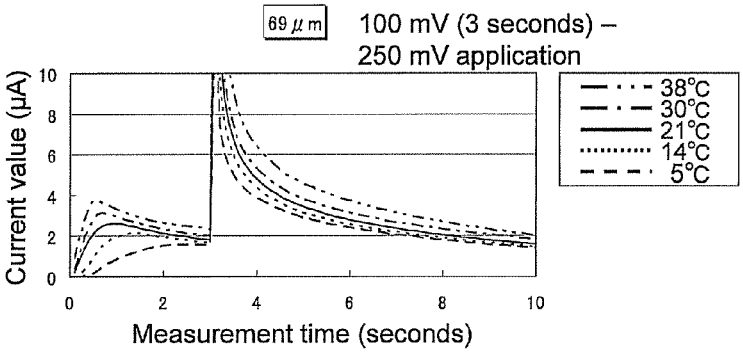


FIG. 52B

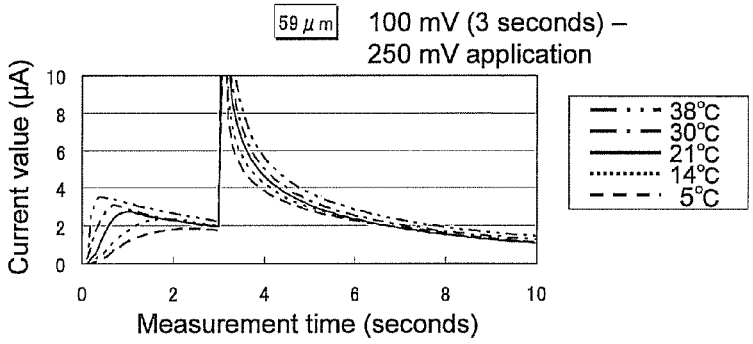


FIG. 52C

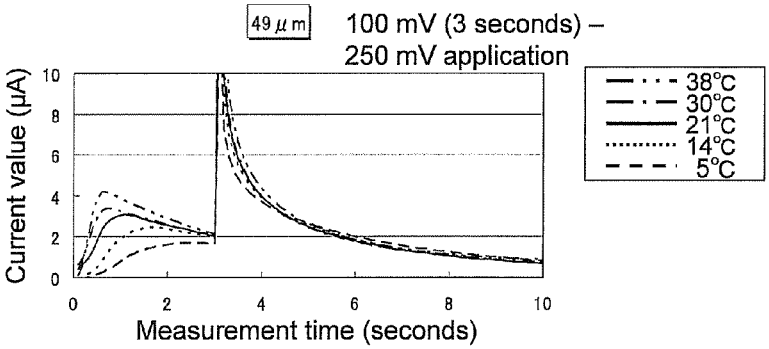


FIG. 52D

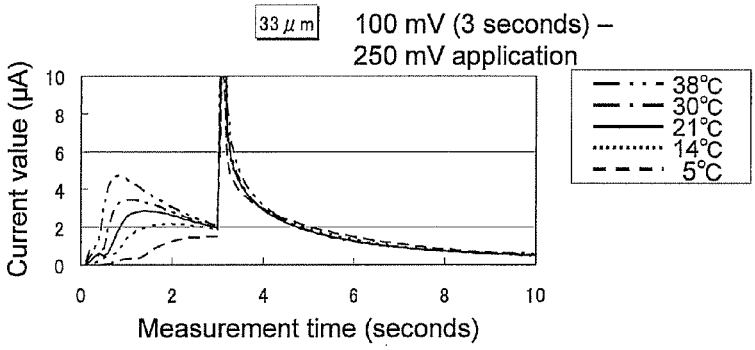


FIG. 53A

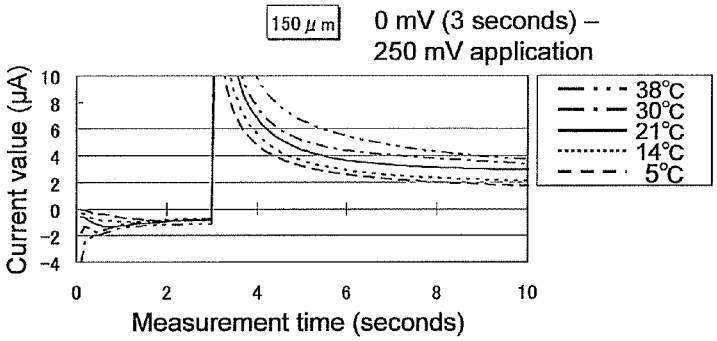


FIG. 53B

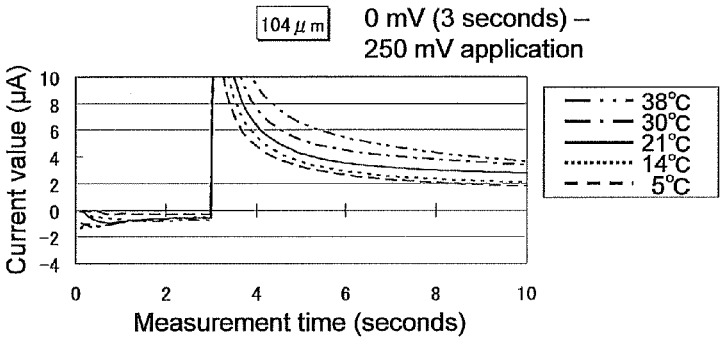


FIG. 53C

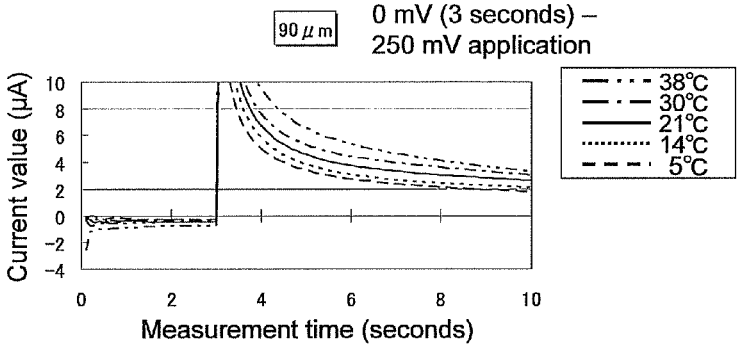


FIG. 53D

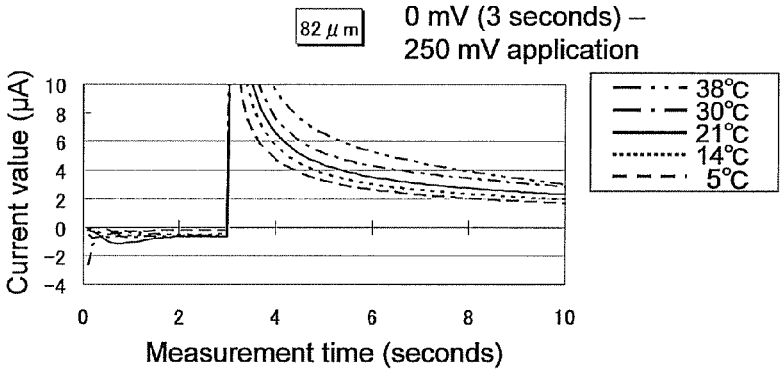


FIG. 54A

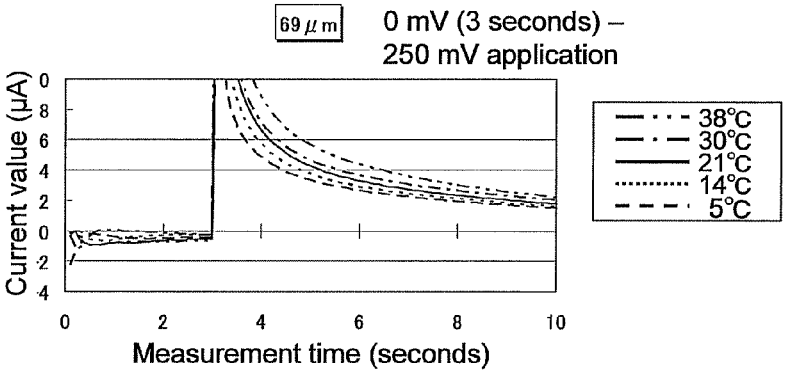


FIG. 54B

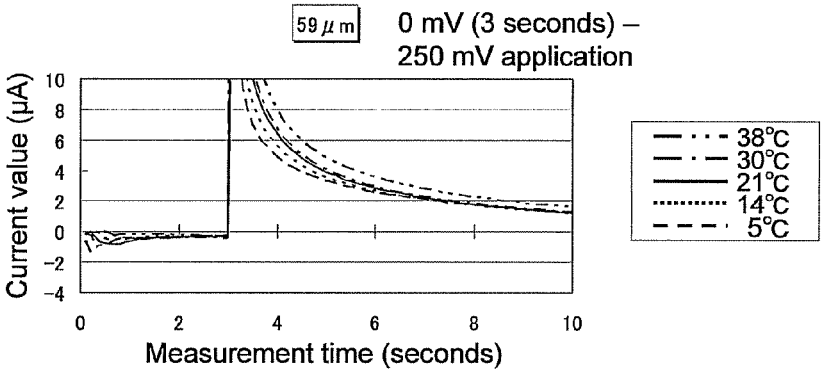


FIG. 54C

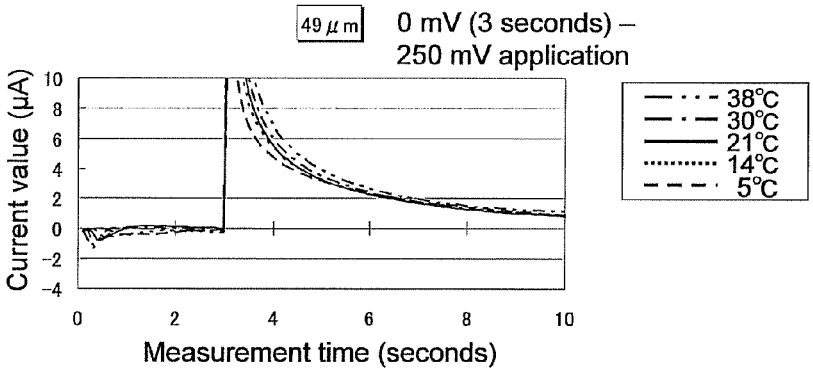


FIG. 54D

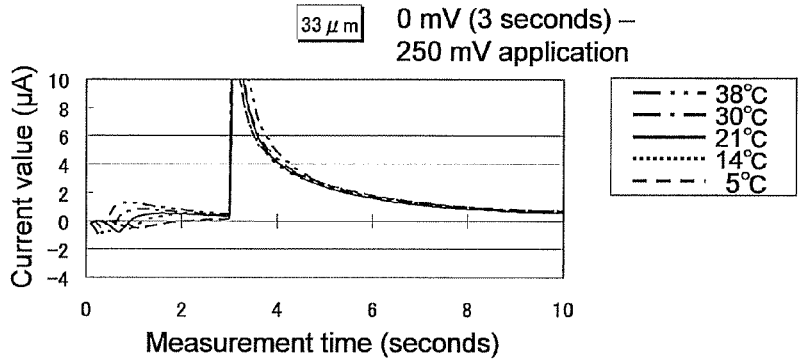


FIG. 55A

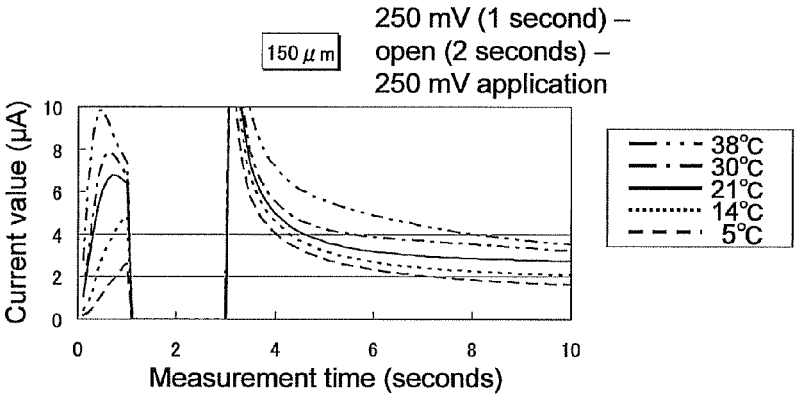


FIG. 55B

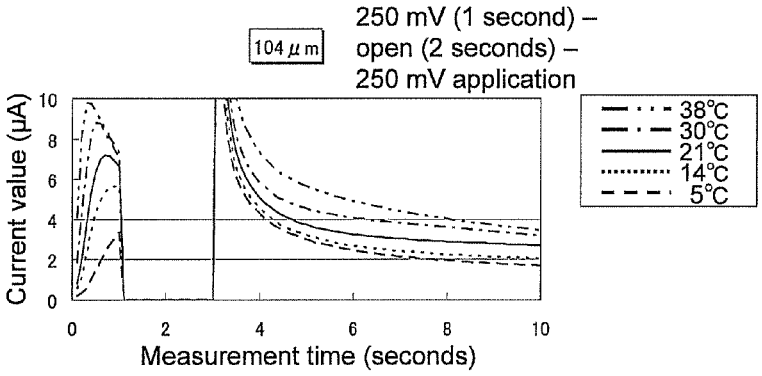


FIG. 55C

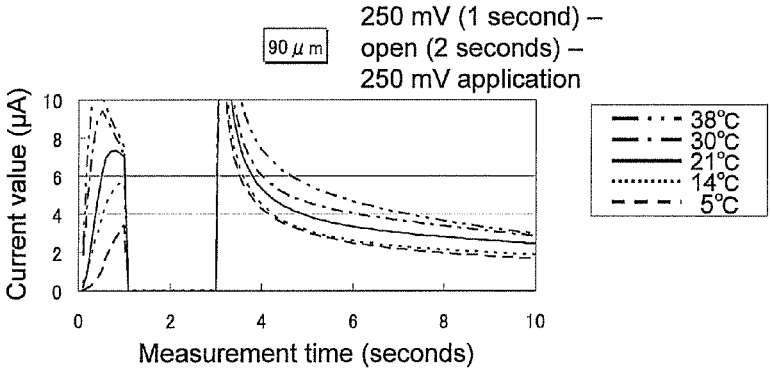


FIG. 55D

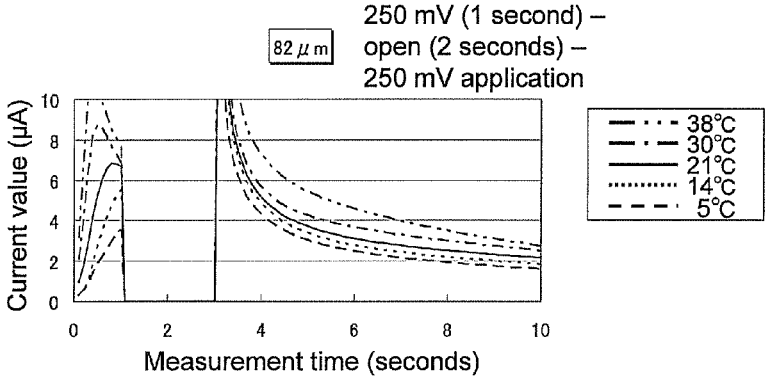


FIG. 56A

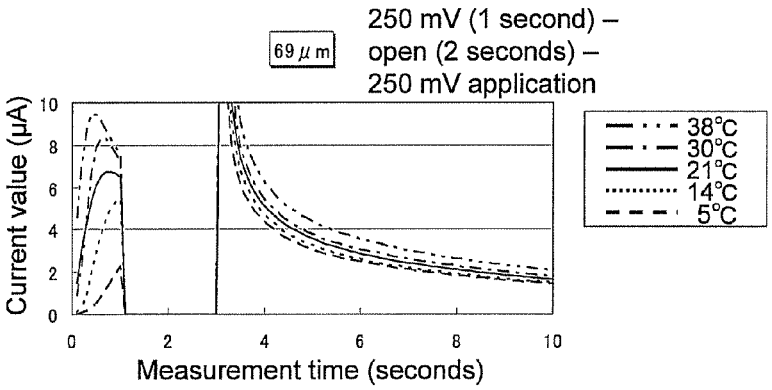


FIG. 56B

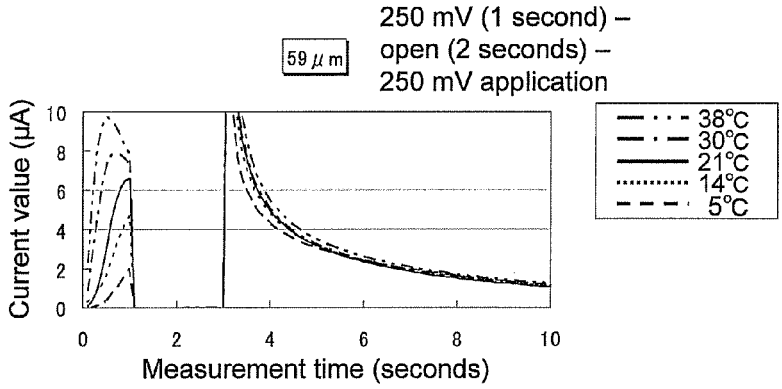
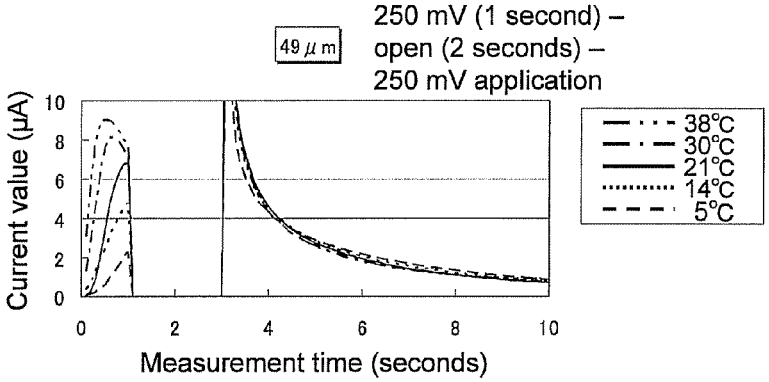


FIG. 56C



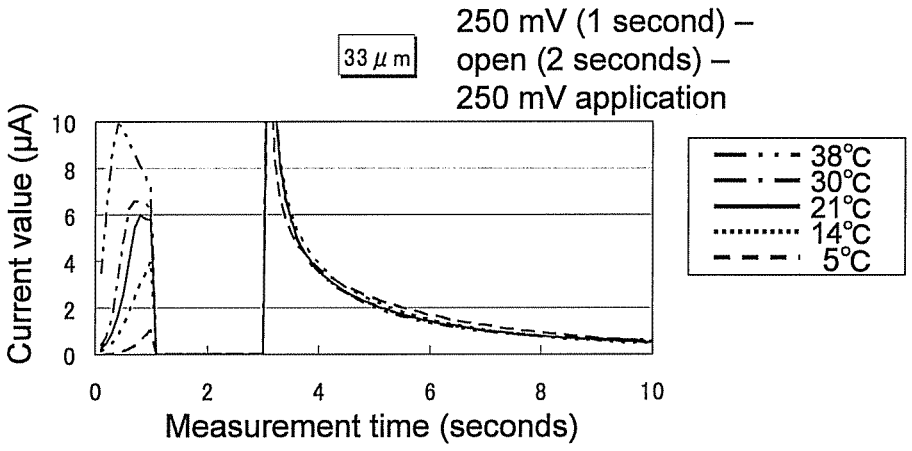

33 μm
250 mV (1 second) –
open (2 seconds) –
250 mV application
Current value (μA)
10
8
6
4
2
0
0
2
4
6
8
10
Measurement time (seconds)
38°C
30°C
21°C
14°C
5°C

FIG. 56D

BIOSENSOR SYSTEM AND METHOD FOR MEASURING CONCENTRATION OF ANALYTE

TECHNICAL FIELD

The present invention relates to a biosensor system and to a method for measuring the concentration of an analyte.

BACKGROUND ART

A portable biosensor system comprising a measurement device with a computer, and a sensor chip that can be installed in this measurement device, has been used in the past to measure the concentration of an analyte in a blood sample, such as the blood glucose concentration (glucose value). The concentration of the analyte is calculated on the basis of the amount of oxidized product and reduced product produced by an enzyme cycling reaction via a redox enzyme in which the analyte serves as the substrate. The speed of the enzyme cycling reaction depends on the temperature of the environment in which the reaction takes place (the reaction temperature). Accordingly, a biosensor system has been proposed that comprises a function of correcting the concentration of an analyte on the basis of the reaction temperature. The reaction temperature is measured, for example, by a temperature sensor disposed in the measurement device (Patent Literature 1).

CITATION LIST

Patent Literature

Patent Literature 1: Japanese Laid-Open Patent Application 2003-156469

SUMMARY

Technical Problem

With the biosensor system of Patent Literature 1, the internal temperature of the measurement device is measured with a temperature sensor. Thus, the measured temperature does not accurately reflect the temperature of the blood sample. Accordingly, error may occur in the measurement of the analyte concentration.

It is an object of the present invention to provide a biosensor system and a concentration measurement method with which error is less likely to be caused by temperature changes.

Solution to Problem

The biosensor system pertaining to a first aspect of the present invention is a biosensor system with which the concentration of an analyte in a liquid sample is measured using a redox enzyme or an electron-transfer mediator, said biosensor system comprising a sensor chip comprising a capillary into which a liquid sample is introduced, whose height is less than the maximum value of the sum of the diffusion distance of the electron-transfer mediator and the diffusion distance of the analyte at the upper limit of the measurement guaranteed temperature of the biosensor system, a plurality of electrodes disposed within the capillary, and a reagent layer that is disposed within the capillary and includes the electron-transfer mediator; a first voltage applicator that applies a first voltage to the electrodes; a concentration measurement section that measures the concentration of the analyte on the basis of the value of the current flowing through the liquid sample during the first voltage application; and a second voltage applicator that applies a second voltage to the electrodes prior to the application of the first voltage, so that the effect of the temperature of the liquid sample on the measurement results of the concentration measurement section will be diminished.

The measurement method pertaining to a second aspect of the present invention is a method for measuring the concentration of an analyte in a liquid sample using a redox enzyme or an electron-transfer mediator, which is executed by a biosensor system having a sensor chip comprising a capillary into which a liquid sample is introduced, whose height is less than the maximum value of the sum of the diffusion distance of the electron-transfer mediator and the diffusion distance of the analyte at the upper limit of the measurement guaranteed temperature of the biosensor system, a plurality of electrodes disposed within the capillary, and a reagent layer that is disposed within the capillary and includes the electron-transfer mediator, said measurement method comprising a first voltage application step of applying a first voltage to the electrodes, a current detection step of detecting the value of current flowing through the liquid sample during the application of the first voltage, a concentration measurement step of measuring the concentration of the analyte on the basis of the current value, and a second voltage application step of applying a second voltage to the electrodes prior to the detection of the current value, so that the temperature of the liquid sample will have less effect on the measurement results of the concentration measurement section.

Advantageous Effects

With the biosensor system and measurement method pertaining to the present invention, the distance that an analyte in a liquid sample can move by diffusion is limited by a capillary. Furthermore, a second voltage is applied to electrodes before a first voltage is applied, which reduces variance in the measurement result caused by temperature.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** is an perspective view of the configuration of a biosensor system pertaining to an embodiment of the present invention;

FIG. **2** is an exploded perspective view of a sensor chip included in the biosensor system in FIG. **1**;

FIG. **3** is a plan view of the sensor chip in FIG. **2**;

FIG. **4** is a schematic diagram of the diffusion distance of an analyte and a mediator;

FIG. **5**A is a diagram illustrating the height of a capillary in the sensor chip pertaining to an embodiment;

FIG. **5**B is a diagram illustrating the height of a capillary in the sensor chip pertaining to another embodiment;

FIG. **6** is a diagram of the internal configuration of a measurement device **101** in the biosensor system in FIG. **1**;

FIG. **7** is a flowchart showing an example of the flow in a method for measuring the concentration of a blood sample with the biosensor system in FIG. **1**;

FIG. **8** is a flowchart showing another example of the flow in a method for measuring the concentration of a blood sample;

FIG. **9** is a flowchart showing yet another example of the flow in a method for measuring the concentration of a blood sample;

FIG. **10**A is a graph of an example of the pattern of voltage application to a sensor chip;

FIG. **10**B is a graph of another example of the pattern of voltage application to a sensor chip;

FIG. **10**C is a graph of yet another example of the pattern of voltage application to a sensor chip;

FIG. **10**D is a graph of yet another example of the pattern of voltage application to a sensor chip;

FIG. **11**A is a graph of the response current value when the glucose concentration of the sample is 100 mg/dL (milligrams per deciliter), neither the application of open circuit voltage nor the application of low voltage is executed, the applied voltage is 250 mV, and the height of the capillary is 150 μm;

FIG. **11**B is a graph of the response current value under the same conditions as in FIG. **11**A, except that the height of the capillary is 100 μm;

FIG. **11**C is a graph of the response current value under the same conditions as in FIG. **11**A, except that the height of the capillary is 59 μm;

FIG. **11**D is a graph of the response current value under the same conditions as in FIG. **11**A, except that the height of the capillary is 33 μm;

FIG. **12**A is a graph of the response current value when 8 seconds have elapsed in FIGS. **11**A to **11**D;

FIG. **12**B is a graph of the variance in the response current value under the various temperature conditions in FIG. **12**A, using the response current value at 21° C. as a reference;

FIG. **13**A is a graph of the response current value when the glucose concentration of the sample is 400 mg/dL, neither the application of open circuit voltage nor the application of low voltage is executed, the applied voltage is 250 mV, and the height of the capillary is 150 μm;

FIG. **13**B is a graph of the response current value under the same conditions as in FIG. **13**A, except that the height of the capillary is 100 μm;

FIG. **13**C is a graph of the response current value under the same conditions as in FIG. **13**A, except that the height of the capillary is 59 μm;

FIG. **13**D is a graph of the response current value under the same conditions as in FIG. **13**A, except that the height of the capillary is 33 μm;

FIG. **14**A is a graph of the response current value when 8 seconds have elapsed in FIGS. **13**A to **13**D;

FIG. **14**B is a graph of the variance in the response current value under the various temperature conditions in FIG. **14**A, using the response current value at 21° C. as a reference;

FIG. **15**A is a graph of the amount of charge obtained by adding up the measurement results for response current value in FIG. **11**A every 0.1 second;

FIG. **15**B is a graph of the amount of charge obtained by adding up the measurement results for response current value in FIG. **11**B every 0.1 second;

FIG. **15**C is a graph of the amount of charge obtained by adding up the measurement results for response current value in FIG. **11**C every 0.1 second;

FIG. **15**D is a graph of the amount of charge obtained by adding up the measurement results for response current value in FIG. **11**D every 0.1 second;

FIG. **16**A is a graph of the amount of charge when 8 seconds have elapsed in FIGS. **15**A to **15**D;

FIG. **16**B is a graph of the variance in the amount of charge under the various temperature conditions in FIG. **16**A, using the amount of charge at 21° C. as a reference;

FIG. **17**A is a graph of the amount of charge obtained by adding up the measurement results for response current value in FIG. **13**A every 0.1 second;

FIG. **17**B is a graph of the amount of charge obtained by adding up the measurement results for response current value in FIG. **13**B every 0.1 second;

FIG. **17**C is a graph of the amount of charge obtained by adding up the measurement results for response current value in FIG. **13**C every 0.1 second;

FIG. **17**D is a graph of the amount of charge obtained by adding up the measurement results for response current value in FIG. **13**D every 0.1 second;

FIG. **18**A is a graph of the amount of charge when 8 seconds have elapsed in FIGS. **17**A to **17**D;

FIG. **18**B is a graph of the variance in the amount of charge under the various temperature conditions in FIG. **18**A, using the amount of charge at 21° C. as a reference;

FIG. **19**A is a graph of the response current value when the glucose concentration of the sample is 100 mg/dL (milligrams per deciliter), the voltage application conditions are open (5 seconds)—250 mV, and the height of the capillary is 150 μm;

FIG. **19**B is a graph of the response current value under the same conditions as in FIG. **19**A, except that the height of the capillary is 100 μm;

FIG. **19**C is a graph of the response current value under the same conditions as in FIG. **19**A, except that the height of the capillary is 59 μm;

FIG. **19**D is a graph of the response current value under the same conditions as in FIG. **19**A, except that the height of the capillary is 33 μm;

FIG. **20**A is a graph of the response current value when 8 seconds have elapsed in FIGS. **19**A to **19**D;

FIG. **20**B is a graph of the variance in the response current value under the various temperature conditions in FIG. **20**A, using the response current value at 21° C. as a reference;

FIG. **21**A is a graph of the response current value when the glucose concentration of the sample is 400 mg/dL (milligrams per deciliter), the voltage application conditions are open (5 seconds)—250 mV, and the height of the capillary is 150 μm;

FIG. **21**B is a graph of the response current value under the same conditions as in FIG. **21**A, except that the height of the capillary is 100 μm;

FIG. **21**C is a graph of the response current value under the same conditions as in FIG. **21**A, except that the height of the capillary is 59 μm;

FIG. **21**D is a graph of the response current value under the same conditions as in FIG. **21**A, except that the height of the capillary is 33 μm;

FIG. **22**A is a graph of the response current value when 8 seconds have elapsed in FIGS. **21**A to **21**D;

FIG. **22**B is a graph of the variance in the response current value under the various temperature conditions in FIG. **22**A, using the response current value at 21° C. as a reference;

FIG. **23**A is a graph of the response current value when the glucose concentration of the sample is 40 mg/dL (milligrams per deciliter), the voltage application conditions are open (1.5 seconds)—250 mV, and the height of the capillary is 150 μm;

FIG. **23**B is a graph of the response current value under the same conditions as in FIG. **23**A, except that the height of the capillary is 100 μm;

FIG. **23**C is a graph of the response current value under the same conditions as in FIG. **23**A, except that the height of the capillary is 59 μm;

FIG. **23**D is a graph of the response current value under the same conditions as in FIG. **23**A, except that the height of the capillary is 33 μm;

FIG. **24**A is a graph of the response current value under the same conditions as in FIG. **23**A, except that the glucose concentration of the sample is 155 mg/dL;

FIG. **24**B is a graph of the response current value under the same conditions as in FIG. **24**A, except that the height of the capillary is 100 μm;

FIG. **24**C is a graph of the response current value under the same conditions as in FIG. **24**A, except that the height of the capillary is 59 μm;

FIG. **24**D is a graph of the response current value under the same conditions as in FIG. **24**A, except that the height of the capillary is 33 μm;

FIG. **25**A is a graph of the response current value under the same conditions as in FIG. **23**A, except that the glucose concentration of the sample is 345 mg/dL;

FIG. **25**B is a graph of the response current value under the same conditions as in FIG. **25**A, except that the height of the capillary is 100 μm;

FIG. **25**C is a graph of the response current value under the same conditions as in FIG. **25**A, except that the height of the capillary is 59 μm;

FIG. **25**D is a graph of the response current value under the same conditions as in FIG. **25**A, except that the height of the capillary is 33 μm;

FIG. **26**A is a graph of the response current value under the same conditions as in FIG. **23**A, except that the glucose concentration of the sample is 600 mg/dL;

FIG. **26**B is a graph of the response current value under the same conditions as in FIG. **26**A, except that the height of the capillary is 100 μm;

FIG. **26**C is a graph of the response current value under the same conditions as in FIG. **26**A, except that the height of the capillary is 59 μm;

FIG. **26**D is a graph of the response current value under the same conditions as in FIG. **26**A, except that the height of the capillary is 33 μm;

FIG. **27**A is a graph of the relation between temperature, glucose concentration, and the current value when 5.5 seconds have elapsed (4 seconds after the start of application of a voltage of 250 mV), when the height of the capillary is 150 μm, on the basis of FIGS. **23**A, **24**A, **25**A, and **26**A;

FIG. **27**B is a graph of the relation between temperature, glucose concentration, and the current value when 5.5 seconds have elapsed (4 seconds after the start of application of a voltage of 250 mV), when the height of the capillary is 100 μm, on the basis of FIGS. **23**B, **24**B, **25**B, and **26**B;

FIG. **27**C is a graph of the relation between temperature, glucose concentration, and the current value when 5.5 seconds have elapsed (4 seconds after the start of application of a voltage of 250 mV), when the height of the capillary is 59 μm, on the basis of FIGS. **23**C, **24**C, **25**C, and **26**C;

FIG. **27**D is a graph of the relation between temperature, glucose concentration, and the current value when 5.5 seconds have elapsed (4 seconds after the start of application of a voltage of 250 mV), when the height of the capillary is 33 μm, on the basis of FIGS. **23**D, **24**D, **25**D, and **26**D;

FIG. **28**A is a graph of the response current value when the glucose concentration of the sample is 40 mg/dL, the voltage application conditions are open (3 seconds)—250 mV, and the height of the capillary is 150 μm;

FIG. **28**B is a graph of the response current value under the same conditions as in FIG. **28**A, except that the height of the capillary is 100 μm;

FIG. **28**C is a graph of the response current value under the same conditions as in FIG. **28**A, except that the height of the capillary is 59 μm;

FIG. **28**D is a graph of the response current value under the same conditions as in FIG. **28**A, except that the height of the capillary is 33 μm;

FIG. **29**A is a graph of the response current value under the same conditions as in FIG. **28**A (the voltage application conditions are open (3 seconds)—250 mV, and the height of the capillary is 150 μm), except that the glucose concentration of the sample is 155 mg/dL;

FIG. **29**B is a graph of the response current value under the same conditions as in FIG. **29**A, except that the height of the capillary is 100 μm;

FIG. **29**C is a graph of the response current value under the same conditions as in FIG. **29**A, except that the height of the capillary is 59 μm;

FIG. **29**D is a graph of the response current value under the same conditions as in FIG. **29**A, except that the height of the capillary is 33 μm;

FIG. **30**A is a graph of the response current value under the same conditions as in FIG. **28**A (the voltage application conditions are open (3 seconds)—250 mV, and the height of the capillary is 150 μm), except that the glucose concentration of the sample is 345 mg/dL;

FIG. **30**B is a graph of the response current value under the same conditions as in FIG. **30**A, except that the height of the capillary is 100 μm;

FIG. **30**C is a graph of the response current value under the same conditions as in FIG. **30**A, except that the height of the capillary is 59 μm;

FIG. **30**D is a graph of the response current value under the same conditions as in FIG. **30**A, except that the height of the capillary is 33 μm;

FIG. **31**A is a graph of the response current value under the same conditions as in FIG. **28**A (the voltage application conditions are open (3 seconds)—250 mV, and the height of the capillary is 150 μm), except that the glucose concentration of the sample is 600 mg/dL;

FIG. **31**B is a graph of the response current value under the same conditions as in FIG. **31**A, except that the height of the capillary is 100 μm;

FIG. **31**C is a graph of the response current value under the same conditions as in FIG. **31**A, except that the height of the capillary is 59 μm;

FIG. **31**D is a graph of the response current value under the same conditions as in FIG. **31**A, except that the height of the capillary is 33 μm;

FIG. **32**A is a graph of the relation between temperature, glucose concentration, and the current value when 7 seconds have elapsed (4 seconds after the start of application of a voltage of 250 mV), when the height of the capillary is 150 μm, on the basis of FIGS. **28**A, **29**A, **30**A, and **31**A;

FIG. **32**B is a graph of the relation between temperature, glucose concentration, and the current value when 7 seconds have elapsed (4 seconds after the start of application of a voltage of 250 mV), when the height of the capillary is 100 μm, on the basis of FIGS. **28**B, **29**B, **30**B, and **31**B;

FIG. **32**C is a graph of the relation between temperature, glucose concentration, and the current value when 7 seconds have elapsed (4 seconds after the start of application of a voltage of 250 mV), when the height of the capillary is 59 μm, on the basis of FIGS. **28**C, **29**C, **30**C, and **31**C;

FIG. **32**D is a graph of the relation between temperature, glucose concentration, and the current value when 7 seconds have elapsed (4 seconds after the start of application of a voltage of 250 mV), when the height of the capillary is 33 μm, on the basis of FIGS. **28**D, **29**D, **30**D, and **31**D;

FIG. **33**A is a graph of the response current value when the glucose concentration of the sample is 100 mg/dL,

neither the application of open circuit voltage nor the application of low voltage is executed, the applied voltage is 250 mV, and the height of the capillary is 150 μm;

FIG. **33**B is a graph of the response current value under the same conditions as in FIG. **33**A, except that the height of the capillary is 104 μm;

FIG. **33**C is a graph of the response current value under the same conditions as in FIG. **33**A, except that the height of the capillary is 90 μm;

FIG. **33**D is a graph of the response current value under the same conditions as in FIG. **33**A, except that the height of the capillary is 82 μm;

FIG. **34**A is a graph of the response current value under the same conditions as in FIG. **33**A, except that the height of the capillary is 69 μm;

FIG. **34**B is a graph of the response current value under the same conditions as in FIG. **33**A, except that the height of the capillary is 59 μm;

FIG. **34**C is a graph of the response current value under the same conditions as in FIG. **33**A, except that the height of the capillary is 49 μm;

FIG. **34**D is a graph of the response current value under the same conditions as in FIG. **33**A, except that the height of the capillary is 33 μm;

FIG. **35**A is a graph of the response current value under the same conditions as in FIG. **33**A, except that the voltage application conditions are open (1 second)—250 mV;

FIG. **35**B is a graph of the response current value under the same conditions as in FIG. **35**A, except that the height of the capillary is 104 μm;

FIG. **35**C is a graph of the response current value under the same conditions as in FIG. **35**A, except that the height of the capillary is 90 μm;

FIG. **35**D is a graph of the response current value under the same conditions as in FIG. **35**A, except that the height of the capillary is 82 μm;

FIG. **36**A is a graph of the response current value under the same conditions as in FIG. **35**A, except that the height of the capillary is 69 μm;

FIG. **36**B is a graph of the response current value under the same conditions as in FIG. **35**A, except that the height of the capillary is 59 μm;

FIG. **36**C is a graph of the response current value under the same conditions as in FIG. **35**A, except that the height of the capillary is 49 μm;

FIG. **36**D is a graph of the response current value under the same conditions as in FIG. **35**A, except that the height of the capillary is 33 μm;

FIG. **37**A is a graph of the response current value under the same conditions as in FIG. **33**A, except that the voltage application conditions are open (1.5 seconds)—250 mV;

FIG. **37**B is a graph of the response current value under the same conditions as in FIG. **37**A, except that the height of the capillary is 104 μm;

FIG. **37**C is a graph of the response current value under the same conditions as in FIG. **37**A, except that the height of the capillary is 90 μm;

FIG. **37**D is a graph of the response current value under the same conditions as in FIG. **37**A, except that the height of the capillary is 82 μm;

FIG. **38**A is a graph of the response current value under the same conditions as in FIG. **37**A, except that the height of the capillary is 69 μm;

FIG. **38**B is a graph of the response current value under the same conditions as in FIG. **37**A, except that the height of the capillary is 59 μm;

FIG. **38**C is a graph of the response current value under the same conditions as in FIG. **37**A, except that the height of the capillary is 49 μm;

FIG. **38**D is a graph of the response current value under the same conditions as in FIG. **37**A, except that the height of the capillary is 33 μm;

FIG. **39**A is a graph of the response current value under the same conditions as in FIG. **33**A, except that the voltage application conditions are open (2 seconds)—250 mV;

FIG. **39**B is a graph of the response current value under the same conditions as in FIG. **39**A, except that the height of the capillary is 104 μm;

FIG. **39**C is a graph of the response current value under the same conditions as in FIG. **39**A, except that the height of the capillary is 90 μm;

FIG. **39**D is a graph of the response current value under the same conditions as in FIG. **39**A, except that the height of the capillary is 82 μm;

FIG. **40**A is a graph of the response current value under the same conditions as in FIG. **39**A, except that the height of the capillary is 69 μm;

FIG. **40**B is a graph of the response current value under the same conditions as in FIG. **39**A, except that the height of the capillary is 59 μm;

FIG. **40**C is a graph of the response current value under the same conditions as in FIG. **39**A, except that the height of the capillary is 49 μm;

FIG. **40**D is a graph of the response current value under the same conditions as in FIG. **39**A, except that the height of the capillary is 33 μm;

FIG. **41**A is a graph of the response current value under the same conditions as in FIG. **33**A, except that the voltage application conditions are open (3 seconds)—250 mV;

FIG. **41**B is a graph of the response current value under the same conditions as in FIG. **41**A, except that the height of the capillary is 104 μm;

FIG. **41**C is a graph of the response current value under the same conditions as in FIG. **41**A, except that the height of the capillary is 90 μm;

FIG. **41**D is a graph of the response current value under the same conditions as in FIG. **41**A, except that the height of the capillary is 82 μm;

FIG. **42**A is a graph of the response current value under the same conditions as in FIG. **41**A, except that the height of the capillary is 69 μm;

FIG. **42**B is a graph of the response current value under the same conditions as in FIG. **41**A, except that the height of the capillary is 59 μm;

FIG. **42**C is a graph of the response current value under the same conditions as in FIG. **41**A, except that the height of the capillary is 49 μm;

FIG. **42**D is a graph of the response current value under the same conditions as in FIG. **41**A, except that the height of the capillary is 33 μm;

FIG. **43**A is a graph of the response current value under the same conditions as in FIG. **33**A, except that the voltage application conditions are open (4 seconds)—250 mV;

FIG. **43**B is a graph of the response current value under the same conditions as in FIG. **43**A, except that the height of the capillary is 104 μm;

FIG. **43**C is a graph of the response current value under the same conditions as in FIG. **43**A, except that the height of the capillary is 90 μm;

FIG. **43**D is a graph of the response current value under the same conditions as in FIG. **43**A, except that the height of the capillary is 82 μm;

FIG. **44**A is a graph of the response current value under the same conditions as in FIG. **43**A, except that the height of the capillary is 69 μm;

FIG. **44**B is a graph of the response current value under the same conditions as in FIG. **43**A, except that the height of the capillary is 59 μm;

FIG. **44**C is a graph of the response current value under the same conditions as in FIG. **43**A, except that the height of the capillary is 49 μm;

FIG. **44**D is a graph of the response current value under the same conditions as in FIG. **43**A, except that the height of the capillary is 33 μm;

FIG. **45**A is a graph of the response current value under the same conditions as in FIG. **33**A, except that the voltage application conditions are open (5 seconds)—250 mV;

FIG. **45**B is a graph of the response current value under the same conditions as in FIG. **45**A, except that the height of the capillary is 104 μm;

FIG. **45**C is a graph of the response current value under the same conditions as in FIG. **45**A, except that the height of the capillary is 90 μm;

FIG. **45**D is a graph of the response current value under the same conditions as in FIG. **45**A, except that the height of the capillary is 82 μm;

FIG. **46**A is a graph of the response current value under the same conditions as in FIG. **45**A, except that the height of the capillary is 69 μm;

FIG. **46**B is a graph of the response current value under the same conditions as in FIG. **45**A, except that the height of the capillary is 59 μm;

FIG. **46**C is a graph of the response current value under the same conditions as in FIG. **45**A, except that the height of the capillary is 49 μm;

FIG. **46**D is a graph of the response current value under the same conditions as in FIG. **45**A, except that the height of the capillary is 33 μm;

FIG. **47**A is a graph of the variance in the response current values measured at 5° C., 14° C., 30° C., and 38° C. when the glucose concentration of the sample is 100 mg/dL, neither the application of open circuit voltage nor the application of low voltage is executed, the applied voltage is 250 mV, and the height of the capillary is 104 μm, using the response current value at 21° C. as a reference (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **47**B is a graph of the variance in the response current value under the same conditions as in FIG. **47**A, except that the height of the capillary is 90 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **47**C is a graph of the variance in the response current value under the same conditions as in FIG. **47**A, except that the height of the capillary is 82 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison)

FIG. **47**D is a graph of the variance in the response current value under the same conditions as in FIG. **47**A, except that the height of the capillary is 69 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison)

FIG. **48**A is a graph of the variance in the response current value under the same conditions as in FIG. **47**A, except that the height of the capillary is 59 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **48**B is a graph of the variance in the response current value under the same conditions as in FIG. **47**A, except that the height of the capillary is 49 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **48**C is a graph of the variance in the response current value under the same conditions as in FIG. **47**A, except that the height of the capillary is 33 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **49**A is a graph of the variance in the response current values measured at 5° C., 14° C., 30° C., and 38° C. when the glucose concentration of the sample is 100 mg/dL, the voltage application conditions are open (2 seconds)—250 mV, and the height of the capillary is 104 μm, using the response current value at 21° C. as a reference (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **49**B is a graph of the variance in the response current value under the same conditions as in FIG. **49**A, except that the height of the capillary is 90 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **49**C is a graph of the variance in the response current value under the same conditions as in FIG. **49**A, except that the height of the capillary is 82 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **49**D is a graph of the variance in the response current value under the same conditions as in FIG. **49**A, except that the height of the capillary is 69 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **50**A is a graph of the variance in the response current value under the same conditions as in FIG. **49**A, except that the height of the capillary is 59 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **50**B is a graph of the variance in the response current value under the same conditions as in FIG. **49**A, except that the height of the capillary is 49 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **50**C is a graph of the variance in the response current value under the same conditions as in FIG. **49**A, except that the height of the capillary is 33 μm (the variance obtained under the same conditions, except that the height of the capillary is 150 μm, is shown for comparison);

FIG. **51**A is a graph of the variance in the response current values when the glucose concentration of the sample is 100 mg/dL, the voltage application conditions are open (3 seconds)—250 mV, and the height of the capillary is 150 μm;

FIG. **51**B is a graph of the response current value under the same conditions as in FIG. **51**A, except that the height of the capillary is 104 μm;

FIG. **51**C is a graph of the response current value under the same conditions as in FIG. **51**A, except that the height of the capillary is 90 μm;

FIG. **51**D is a graph of the response current value under the same conditions as in FIG. **51**A, except that the height of the capillary is 82 μm;

FIG. **52**A is a graph of the response current value under the same conditions as in FIG. **51**A, except that the height of the capillary is 69 μm;

FIG. **52**B is a graph of the response current value under the same conditions as in FIG. **51**A, except that the height of the capillary is 59 μm;

FIG. **52**C is a graph of the response current value under the same conditions as in FIG. **51**A, except that the height of the capillary is 49 μm;

FIG. **52**D is a graph of the response current value under the same conditions as in FIG. **51**A, except that the height of the capillary is 33 μm;

FIG. **53**A is a graph of the response current value when the glucose concentration of the sample is 100 mg/dL, the voltage application conditions are 0 mV (3 seconds)—250 mV, and the height of the capillary is 150 μm;

FIG. **53**B is a graph of the response current value under the same conditions as in FIG. **53**A, except that the height of the capillary is 104 μm;

FIG. **53**C is a graph of the response current value under the same conditions as in FIG. **53**A, except that the height of the capillary is 90 μm;

FIG. **53**D is a graph of the response current value under the same conditions as in FIG. **53**A, except that the height of the capillary is 82 μm;

FIG. **54**A is a graph of the response current value under the same conditions as in FIG. **53**A, except that the height of the capillary is 69 μm;

FIG. **54**B is a graph of the response current value under the same conditions as in FIG. **53**A, except that the height of the capillary is 59 μm;

FIG. **54**C is a graph of the response current value under the same conditions as in FIG. **53**A, except that the height of the capillary is 49 μm;

FIG. **54**D is a graph of the response current value under the same conditions as in FIG. **53**A, except that the height of the capillary is 33 μm;

FIG. **55**A is a graph of the response current value when the glucose concentration of the sample is 100 mg/dL, the voltage application conditions are 250 mV (1 second)—open (2 seconds)—250 mV, and the height of the capillary is 150 μm;

FIG. **55**B is a graph of the response current value under the same conditions as in FIG. **55**A, except that the height of the capillary is 104 μm;

FIG. **55**C is a graph of the response current value under the same conditions as in FIG. **55**A, except that the height of the capillary is 90 μm;

FIG. **55**D is a graph of the response current value under the same conditions as in FIG. **55**A, except that the height of the capillary is 82 μm;

FIG. **56**A is a graph of the response current value under the same conditions as in FIG. **55**A, except that the height of the capillary is 69 μm;

FIG. **56**B is a graph of the response current value under the same conditions as in FIG. **55**A, except that the height of the capillary is 59 μm;

FIG. **56**C is a graph of the response current value under the same conditions as in FIG. **55**A, except that the height of the capillary is 49 μm; and

FIG. **56**D is a graph of the response current value under the same conditions as in FIG. **55**A, except that the height of the capillary is 33 μm.

DESCRIPTION OF EMBODIMENTS

A biosensor system **100** featuring a sensor chip **200** pertaining to an embodiment of the present invention will now be described.

1. Configuration of Biosensor System

The biosensor system **100** pertaining to this embodiment is a system that includes a sensor for measuring the concentration of an analyte included in a liquid sample. As shown in FIG. **1**, the biosensor system **100** has a measurement device **101** and the sensor chip **200**.

The liquid sample is not limited to being any particular sample, and a variety of samples can be used, such as blood, perspiration, urine, and other such biologically derived liquid samples (biological samples); liquid samples that come from a river, the ocean, a lake, or another such environment; and liquid samples that come from food. The biosensor system **100** is preferably applied to a biological sample, and particularly to blood.

Nor is the analyte (the substance to be measured) limited to any particular substance, and the sensor chip **200** can accommodate any of a variety of substances, by changing the enzyme or the like in a reagent layer **20** (discussed below). Examples of analytes in a blood sample include substances excluding blood cells, such as glucose, albumin, lactic acid, bilirubin, and cholesterol.

The measurement device **101** has in its side wall a mounting opening **102**, which is a rectangular hole. The sensor chip **200** can be connected in a removable state to the mounting opening **102**. A display section **103** that displays measurement results is disposed in the approximate center of one main face of the measurement device **101**. The configuration of the measurement device **101** will be discussed in detail below.

2. Sensor Chip

2-1. Configuration of Sensor Chip

The sensor chip **200** is a disposable sensor chip that is discarded after a single use. As shown in FIGS. **2** and **3**, the sensor chip **200** comprises an insulated board **201**, a spacer **202**, and a cover **203**. The cover **203** is disposed on the insulated board **201** with the spacer **202** in between. The insulated board **201**, the spacer **202**, and the cover **203** are integrated adhesively, by heat fusion, or the like, for example.

The materials of the insulated board **201**, the spacer **202**, and the cover **203** can be polyethylene terephthalate, polycarbonate, polyimide, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polyoxymethylene, monomer cast nylon, polybutylene terephthalate, methacrylic resin, ABS resin, and other such resins, and glass.

The sensor chip **200** further comprises a capillary **40** (FIG. **3**). The capillary **40** holds a liquid sample. The capillary **40** is constituted by a cut-out **204** in the spacer **202**. The capillary **40** has a shape that is longer in the long-side direction of the sensor chip **200**. The capillary **40** leads to the outside of the sensor chip **200** at one end of the spacer **202** (the end on the left in FIGS. **2** and **3**). In other words, the sensor chip **200** comprises an introduction port **17** that opens outward, and the capillary **40** is connected to and communicates with the introduction port **17**. The volume of the liquid sample introduced into the capillary **40** is 1 μL or less, for example.

Three electrodes **11** to **13** are provided on the surface of the insulated board **201**. The electrode **11** is sometimes called a working electrode, the electrode **12** a counter electrode, and the electrode **13** a detecting electrode. A portion of each of the electrodes **11** to **13** is disposed within the capillary **40**. The electrodes **11** to **13** are disposed so as to be aligned in the order of the electrode **12**, the electrode **11**, the electrode **12**, and the electrode **13**, from the introduction port **17** toward the interior of the capillary **40**. That

is, in FIG. **5**A, the electrodes are disposed so as to be opposite each other in the planar direction of the insulated board **201**.

However, as shown in FIG. **5**B, the electrode **11**, the electrode **12**, and the electrode **13** may be disposed three-dimensionally. For instance, the electrode **12** may be provided at a location opposite the capillary **40** on the lower face of the cover **203**, and the electrode **11** and the electrode **13** may be provided on the insulated board **201**.

There are no particular restrictions on the number of electrodes **11** to **13** used in the sensor chip **200**. The number of each of the electrodes may be two or more.

The material of the electrodes **11** to **13** may be palladium, platinum, gold, silver, titanium, copper, nickel, carbon, or any other known conductive material.

Also, the electrodes **11** to **13** are lined to leads **110**, **120**, and **130**, respectively. The leads **110**, **120**, and **130** are provided on the insulated board **201**. One end of the insulated board **201** is not covered by the spacer **202** and the cover **203**. One end of the leads **110**, **120**, and **130** is not covered on the insulated board **201**, and is exposed outside the sensor chip **200**. The measurement device **101** applies voltage to the electrodes **11** to **13** via the leads **110**, **120**, and **130**.

An air vent **16** is provided to the cover **203** at a location facing the inner part of the cut-out **204** (the opposite side from the introduction port **17**) that forms the capillary **40**. Because the air vent **16** is provided, the liquid sample introduced into the capillary **40** flows under capillary action and in rate-limiting fashion to a detector constituted by the electrodes **11** to **13** and the reagent layer **20**. Thus, the air vent **16** ensures the deposition of a blood sample (biological sample), and improves measurement stability.

Also, the faces on the inside the capillary **40** may be given a hydrophilic treatment or formed from a hydrophilic material. This facilitates the deposition (intake) of the liquid sample and improves reliability.

The reagent layer **20** is placed on the electrodes **11** to **13** between the insulated board **201** and the spacer **202**.

The reagent layer **20** is formed by precoating the insulated board **201** with a reagent that includes an electrolyte. The reagent layer **20** is formed so as to cover the overlapping portion of the electrodes **11**, **12**, and **13** on the insulated board **201**. The reagent layer **20** contains an electron-transfer mediator (hereinafter referred to simply as a "mediator") and a redox enzyme in which the analyte in the liquid sample serves as the substrate.

A redox enzyme in which the analyte serves as the substrate can be used favorably as the enzyme. Examples of this enzyme include glucose oxidase and glucose dehydrogenase when the analyte is glucose; lactic acid oxidase and lactic acid dehydrogenase when the analyte is lactic acid; cholesterol esterase and cholesterol oxidase when the analyte is cholesterol; and bilirubin oxidase when the analyte is bilirubin. Other examples of analyte include triglyceride and uric acid.

The mediator is a substance having the function of transferring electrons produced by an enzyme reaction to the electrodes. One or more types of mediator selected from the group consisting of potassium ferricyanide, p-benzoquinone, p-benzoquinone derivatives, oxide-type phenazine methosulfate, methylene blue, ferricinium, and ferricinium derivatives can be used favorably, for example.

The amount of redox enzyme in the reagent layer will vary with the type of enzyme and so forth, in general, 0.01 to 100 units (U) is favorable, with 0.05 to 10 U being preferable, and 0.1 to 5 U being even better.

The reagent layer **20** may contain a water-soluble polymer compound in order to improve the moldability of the reagent layer. This water-soluble polymer compound may be one or more types selected from among carboxymethyl cellulose and salts thereof; hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, ethyl hydroxyethyl cellulose, carboxyethyl cellulose, and salts thereof; polyvinyl alcohol, polyvinylpyrrolidone, polylysine, and other such polyamino acids; polystyrenesulfonic acid and salts thereof; gelatin and derivatives thereof; polyacrylic acid and salts thereof; polymethacrylic acid and salts thereof; starch and derivatives thereof; maleic anhydride polymers and salts thereof; and agarose gel and derivatives thereof.

2-2. Height of Capillary **40**

The system inside the capillary **40** into which the liquid sample is introduced is a diffusion system including a liquid and a diffusant (analyte and mediator, etc.) The liquid here could also be called a diffusion medium or a dispersion medium.

The diffusion distance d of the various diffusants in the liquid is expressed by the following formula (1).

[First Mathematical Formula]

$$d=\sqrt{zDt} \tag{1}$$

z: a constant

D: diffusion coefficient

t: time

The constant z is an arbitrarily selected value. The constant z can vary with the experiment conditions, and can vary according to the definition of the distribution of the distance over which a diffusant is diffused. The constant z is generally set to a range of $1 \leq z \leq 4$. More specifically, the constant z may be defined as 1, 2, π, or 4. In the field of electrochemistry, $z=\pi$ is sometimes used as an example, so we will use $z=\pi$ in the following description.

The diffusion coefficient D is expressed by a Stokes-Einstein relation (the following formula (2)).

[Second Mathematical Formula]

$$D = \frac{kT}{6\pi\mu r} \tag{2}$$

k: Boltzmann constant

T: absolute temperature

μ: viscosity

r: radius of diffused molecules

Thus, based on Formulas 1 and 2, the diffusion distance d is expressed by the following formula (3).

[Third Mathematical Formula]

$$d = \sqrt{\frac{tkT}{6\pi r}} \tag{3}$$

That is, in general, when the temperature rises, the diffusion distance increases.

Furthermore, in a system in which the viscosity μ is dependent on temperature, the viscosity μ is expressed by an Andrade formula (4).

[Fourth Mathematical Formula]

$$\mu = A\exp\left(\frac{E}{RT}\right) \quad (4)$$

A: proportional constant
E: fluid activation energy
R: gas constant
T: absolute temperature

If we plug the above-mentioned Formula 3 into the above-mentioned Formula 4, we obtain the following formula (5).

[Fifth Mathematical Formula]

$$d = \sqrt{\frac{tkT}{6\mu r}} = \sqrt{\frac{tkT}{6rA\exp\left(\frac{E}{RT}\right)}} \quad (5)$$

Here, if we assume that:

[Sixth Mathematical Formula]

$$\sqrt{\frac{k}{6rA}} = B \quad (6)$$

B: constant term

then the diffusion distance d is expressed by the following formula (7).

[Seventh Mathematical Formula]

$$d = B\sqrt{\frac{tT}{\exp\left(\frac{E}{RT}\right)}} \quad (7)$$

In the above-mentioned Formula 7, when the temperature T rises, the exp(E/RT) of the denominator decreases, so there is a further increase in the diffusion distance d.

In general, the fluid activation energy E is large in a high-viscosity liquid, so the viscosity μ is susceptible to the effect of the temperature T. As a result, the higher is the viscosity of the liquid sample, the more susceptible are the diffusion coefficient D and the diffusion distance d to the effect of the temperature T. For example, when the temperature T rises, the viscosity μ decreases and the diffusion coefficient D and the diffusion distance d increase.

As shown in FIG. **4**, an analyte **51** diffuses into the interior of the reagent layer **20**, and transfers electrons through an enzyme reaction to a mediator **54**. The mediator **54** diffuses to the working electrode **11**.

If we let D_A be the diffusion constant of the analyte **51**, and let t_A be the diffusion time it takes for the analyte to transfer electrons to the mediator, then the diffusion distance d_A of the analyte **51** is expressed by the following formula (8). The diffusion time t_A is an arbitrarily set numerical value.

[Eighth Mathematical Formula]

$$d_A = \sqrt{\pi D_A t_A} \quad (8)$$

Similarly, if we let D_M be the diffusion constant of the mediator **54**, and let t_M be the diffusion time it takes for the mediator **54** to transfer electrons to the working electrode **11**, then the diffusion distance d_M of the mediator **54** is expressed by the following formula (9). The diffusion time t_M is also an arbitrarily set numerical value.

[Ninth Mathematical Formula]

$$d_M = \sqrt{\pi D_M t_M} \quad (9)$$

Based on the above-mentioned Formulas 8 and 9, the total diffusion distance d_T until the analyte **51** is detected as a current response is expressed by the following formula (10).

[Tenth Mathematical Formula]

$$d_T = \sqrt{\pi D_A t_A} + \sqrt{\pi D_M t_M} \quad (10)$$

The time until the analyte **51** is detected as a current response can also be expressed by (t_A+t_M). Thus, if we let t_{mes} be the measurement time, the analyte **51** will be detected within the measurement time t_{mes} if the measurement time t_{mes} satisfies the relation $t_{mes} \geq t_A+t_M$. That is, in this case the maximum value of (t_A+t_M) is t_{mes}.

If the diffusion time t_M of the mediator **54** is sufficiently short with respect to the diffusion time t_A of the analyte **51**, the system can be considered to be one in which only the analyte **51** moves one phase. Here, the maximum value d_L of the total diffusion distance d_T is expressed by the following formula (11).

[Eleventh Mathematical Formula]

$$d_L = \sqrt{\pi D_A t_A} = \sqrt{\pi D_A t_{mes}} \quad (11)$$

Since an enzyme is necessary for electron acceptance between the analyte **51** and the mediator **54**, the diffusion distance d_M of the mediator **54** that has taken electrons is equal to the distance that the enzyme has diffused from the working electrode **11**. In general, the diffusion constant of an enzyme is far smaller than the diffusion coefficient D_A of the analyte **51** and the diffusion coefficient D_M of the mediator **54**. Accordingly, the enzyme can be considered to be in a state of having stopped near the working electrode **11**. Also, since the diffusion coefficient D_M of the mediator **54** is extremely short, the diffusion time t_M of the mediator can generally be ignored.

On the other hand, when the diffusion time t_M of the mediator is long, the diffusion system is considered to be one in which two kinds of diffusant move one phase. The maximum value d_L of the total diffusion distance d_T is derived when the formula $t_{mes}=t_A+t_M$ is satisfied in the above-mentioned Formula 10.

Furthermore, when the liquid sample is separated into a plurality of phases, such as when a membrane filter is provided over the reagent layer **20**, the diffusion system inside the capillary **40** will be a system in which the diffusant moves a plurality of phases (n number of phases). Thus, if the diffusion time t_M of the mediator **54** is sufficiently short with respect to the diffusion time t_A of the analyte **51**, the diffusion constant and diffusion time of the analyte **51** are defined for each phase, and the total diffusion distance d_T is expressed by the following formula (12).

[Twelfth Mathematical Formula]

$$d_T = \sum_{k=1}^{n} \sqrt{\pi D_k t_k} \quad (12)$$

(where n is an integer of 2 or more)

Here, if the following formula (13) is satisfied, the maximum value d_L of the total diffusion distance d_T can be derived.

[Thirteenth Mathematical Formula]

$$t_{mes} = \sum_{k=1}^{n} t_k \quad (13)$$

On the other hand, if the diffusion time t_M of the mediator is long, the diffusion system can be considered to be one in which two kinds of diffusant move a plurality of phases (n number of phases), the diffusion constant and diffusion time of the analyte **51** and the mediator **54** are defined for each phase, and the total diffusion distance d_T is expressed by the following formula (14).

[Fourteenth Mathematical Formula]

$$d_T = \sum_{k=1}^{n} \sqrt{\pi D_k t_k} + \sum_{j=1}^{n} \sqrt{\pi D_j t_j} \quad (14)$$

(where n is an integer of 2 or more)

Here, if the following formula (15) is satisfied, the maximum value d_L of the total diffusion distance d_T can be derived.

[Fifteenth Mathematical Formula]

$$t_{mes} = \sum_{k=1}^{n} t_k + \sum_{j=1}^{n} t_j \quad (15)$$

The formulas given above are formulas applied to systems of infinite diffusion. A system of infinite diffusion corresponds to when the height H of the capillary **40** is set high. On the other hand, when the height H is set low, the diffusion system inside the capillary **40** becomes a system of finite diffusion. In this case, the range over which the analyte **51** can diffuse is limited by the height H.

Whether or not the height H is greater than the maximum value d_L of the total diffusion distance d_T becomes a boundary for the diffusion system inside the capillary **40** will be of finite diffusion or infinite diffusion. Specifically, when the diffusion time t_M of the mediator **54** is sufficiently short with respect to the diffusion time t_A of the analyte **51**, the inside of the capillary **40** becomes a system of finite diffusion when the height H satisfies the following formula (16).

[Sixteenth Mathematical Formula]

$$\sqrt{\pi D_A t_A} = \sqrt{\pi D_A t_{mes}} > H \quad (16)$$

On the other hand, when the diffusion time t_M of the mediator **54** is long, and the diffusion system inside the capillary **40** is one in which two kinds of diffusant move one phase, then the diffusion system inside the capillary **40** will be a system of finite diffusion when the height H satisfies the following formula (17) under a condition of $t_{mes} = t_A + t_M$.

[Seventeenth Mathematical Formula]

$$\sqrt{\pi D_A t_A} + \sqrt{\pi D_M t_M} > H \quad (17)$$

Also, when the system inside the capillary **40** is one in which the diffusion time t_M of the mediator **54** is sufficiently short with respect to the diffusion time t_A of the analyte **51**, and the analyte **51** moves a plurality of phases (n number of phases), then the diffusion system inside the capillary **40** will be a system of finite diffusion when the height H satisfies the following formula (18) under the condition of the above-mentioned Formula 13.

[Eighteenth Mathematical Formula]

$$\sum_{k=1}^{n} \sqrt{\pi D_k t_k} > H \quad (18)$$

Furthermore, when the system inside the capillary **40** is one in which the diffusion time t_M of the mediator **54** is long, and two kinds of diffusant move a plurality of phases (n number of phases), then the diffusion system inside the capillary **40** will be a system of finite diffusion when the height H satisfies the following formula (19) under the condition of the above-mentioned Formula 15.

[Nineteenth Mathematical Formula]

$$\sum_{k=1}^{n} \sqrt{\pi D_k t_k} + \sum_{j=1}^{n} \sqrt{\pi D_j t_j} > H \quad (19)$$

The diffusion coefficient D is found using experiment variables and current values and using polarography, a rotating disk electrode method, a potential sweep method, a potential step method, or another such method in the field of electrochemistry. The diffusion coefficient D is also found by a measurement method based on something other than electrochemistry, such as a Taylor dispersion method, a nuclear magnetic resonance-oblique magnetic field method, or the like. In general, the diffusion coefficient of the analyte is 1×10^{-5} $cm^2 \cdot s^{-1}$ or less, and the diffusion coefficient of the mediator is also 1×10^{-5} $cm^2 \cdot s^{-1}$ or less.

As shown in FIG. **5**A, the height H of the capillary **40** is, in more specific terms, the distance from the working electrode **11** to the inner face of the cover **203** (the opposite face from the working electrode **11**). That is, the height H may be the thickness of the spacer **202**, or may be a value obtained by adding the thickness of the reagent layer **20** to the thickness of the spacer **202**.

The height H is set so that the diffusion system inside the capillary **40** will be a system of finite diffusion. The range of the height H here is as described through reference to Formulas 16 to 19 above. As discussed above, the diffusion distance d is a function of temperature. Thus, the height H is preferably set to be less than the maximum value d_L of the total diffusion distance d_T found at the upper limit of the measurement guaranteed temperature of the biosensor system **100**. Thus setting the height H has the effect of minimizing the variance in the measurement results at high temperature with the biosensor system **100**. More preferably,

the height H is set to be less than the maximum value d_L of the total diffusion distance d_T found at the lower limit of the measurement guaranteed temperature of the biosensor system **100**. Thus setting the height H has the advantage that concentration can be measured over a wide range of temperatures using a single calibration curve with the biosensor system **100**.

The layout of the working electrode **11** and the counter electrode **12** is not limited to one in which they are opposite each other in the planar direction of the insulated board **201** as in FIG. **5**A. For instance, the working electrode **11** and the counter electrode **12** may be disposed opposite each other in the height H direction of the capillary **40**. A specific configuration is shown in FIG. **5**B. In the example shown in FIG. **5**B, the working electrode **11** is disposed on the insulated board **201**, and the counter electrode **12** is disposed on the face of the cover **203** that is opposite the insulated board **201**. With this layout, the height H is the distance between the working electrode **11** and the counter electrode **12**. Again with the layout in FIG. **5**B, the height H is preferably within the range discussed above.

With the configurations in both FIG. **5**A and FIG. **5**B, the overall height of the capillary **40** does not have to be within the above-mentioned range, as long as the distance from the working electrode **11** to the portion opposite the working electrode **11** (the cover **203** in FIG. **5**A, and the counter electrode **12** in FIG. **5**B) is within the above-mentioned range.

3. Measurement Device **101**

As shown in FIG. **6**, the measurement device **101** has a control circuit **300** in addition to the constitution discussed above. The control circuit **300** applies voltage between at least two electrodes selected from among the electrodes **11** to **13** of the sensor chip **200** (see FIGS. **2** and **3**).

More specifically, as shown in FIG. **6**, the control circuit **300** has three connectors **301***a*, **301***b*, and **301***c*, a switching circuit **302**, a current/voltage conversion circuit **303**, an analog/digital conversion circuit (hereinafter referred to as an A/D conversion circuit) **304**, a reference voltage source **305**, and a computer **306**. The control circuit **300** can switch the voltage applied to one electrode, via the switching circuit **302**, so that this electrode can be used as a positive or negative pole.

As shown in FIG. **6**, the connectors **301***a*, **301***b*, and **301***c* are connected to the counter electrode **12**, the detection electrode **13**, and the working electrode **11**, respectively, in a state in which the sensor chip **200** is inserted into the mounting opening **102**.

The switching circuit **302** can switch the electrode connected to the reference voltage source **305**, and can switch the amount of voltage applied to the electrodes.

The current/voltage conversion circuit **303** receives from the computer **306** a signal directing the acquisition of a current value, and thereby converts the amount of current flowing between two electrodes connected to the current/voltage conversion circuit **303** into a voltage value. The converted voltage value is converted by the A/D conversion circuit **304** into a digital value, inputted to the computer **306**, and stored in the memory of the computer **306**.

The computer **306** comprises a known central processing unit (CPU) and a storage unit. Examples of the storage unit include a HDD (hard disk drive), ROM (read only memory), and RAM (random access memory). The storage unit stores a calibration curve that correlates the analyte concentration in a blood sample with the current value between the working electrode **11** and the counter electrode **12**. The computer **306** can refer to the calibration curve to compute the concentration of the analyte in the blood sample.

Also, in addition to having a function of calculating the concentration of analyte as mentioned above, the computer **306** also controls the switching circuit **302**, takes input from the A/D conversion circuit **304**, controls the voltage of the reference voltage source **305**, controls the timing of voltage application during concentration measurement, measures the application duration, etc. (timer function), outputs display data to the display section **103**, and communicates with external devices, and therefore controls the entire measurement device.

The various functions of the computer **306** can be realized by the CPU by reading and executing programs held in the storage unit.

4. Measurement of Analyte Concentration

When the sensor chip **200** is used, the user deposits a liquid sample at the introduction port **17**. For example, when the biosensor system **100** is used to measure a glucose value, the user pricks his finger, hand, arm, or the like, squeezes out a small amount of blood, and deposits this blood as a liquid sample for measurement.

The liquid sample deposited at the introduction port **17** moves by capillary action through the capillary **40** toward the back of the sensor chip **200**, and reach the electrodes **11** to **13**.

The measurement of analyte concentration performed by the biosensor system **100** will be described.

The operation shown in FIG. **7** begins when the sensor chip **200** is mounted in the mounting opening **102** of the measurement device **101**. First, the detection electrode **13** is connected to the current/voltage conversion circuit **303** via the connector **301***b* by the switching circuit **302** at a command from the CPU of the computer **306**, and the counter electrode **12** is connected to the reference voltage source **305** via the connector **301***a*. After this, a specific voltage is applied between the two electrodes at a command from the CPU (step S**11**). This voltage is preferably 0.01 to 2.0 V, and more preferably 0.1 to 1.0 V, and even more preferably 0.2 to 0.5 V, when the detection electrode **13** is a positive pole and the counter electrode **12** is a negative pole. This voltage is applied from the point when the sensor chip is inserted into the measurement device **101** until the blood sample is introduced deep into the capillary **40**.

When the blood sample is introduced from the introduction port **17** of the sensor chip **200** into the capillary **40**, current flows between the detection electrode **13** and the counter electrode **12**. The CPU identifies the amount of increase in current per unit of time before and after the blood sample is introduced, and thereby detects that the capillary **40** has been filled with the blood sample. The value of this current is converted into a voltage value by the current/voltage conversion circuit **303**, after which it is converted into a digital value by the A/D conversion circuit **304**, and inputted to the CPU. The CPU detects that the blood sample has been introduced deep into the capillary on the basis of this digital value.

When a sample is thus detected (Yes in step S**12**), step S**13** is executed. Specifically, at a command from the CPU of the computer **306**, the switching circuit **302** disconnects the detection electrode **13** from the current/voltage conversion circuit **303**, connects the working electrode **11** and the reference voltage source **305**, and connects the counter electrode **12** and the current/voltage conversion circuit **303**.

More specifically, the working electrode **11** is connected to the current/voltage conversion circuit **303** via the connector **301***c*, and the counter electrode **12** is connected to the reference voltage source **305** via the connector **301***a*. An open circuit voltage is then applied between the working electrode **11** and the counter electrode **12**. The phrase "open circuit voltage is applied" may be restated as "the voltage application is switched off."

As shown in FIG. **10**A, the application time T_1 of the open circuit voltage in step **S13** is not limited to any specific value, as long as the effect of temperature on the concentration measurement results can be reduced. The time T_1 is set to 0.5 to 15 seconds, for example, and preferably 1 to 10 seconds, and more preferably 1 to 5 seconds, and even more preferably about 2 to 3 seconds.

Next, a measurement voltage V_{mes} is applied between the working electrode **11** and the counter electrode **12** under the control of the computer **306** (step **S14**). The amount of measurement voltage V_{mes} applied here can be varied according to the type of mediator and the type of analyte being measured.

When the measurement voltage V_{mes} is applied, the value of the current flowing between the working electrode **11** and the counter electrode **12** is acquired (step **S15**). A signal directing the acquisition of a current value is sent from the CPU of the computer **306** to the current/voltage conversion circuit **303**. The value of the current that flows between the electrodes as a result of the application of the measurement voltage V_{mes} is converted by the current/voltage conversion circuit **303** into a voltage value. After this, the converted voltage value is converted by the A/D conversion circuit **304** into a digital value and inputted to the CPU, then held in the memory of the computer **306**. In this way, the current value at the time of measurement voltage V_{mes} application is acquired in a state of having been converted into a digital voltage value.

The computer **306** calculates the concentration of analyte on the basis of the above-mentioned calibration curve and the digital value thus stored (step **S16**).

The effect of thus applying open circuit voltage prior to the application of the measurement voltage V_{mes} is that the concentration measurement results are less likely to be affected by temperature.

In the above embodiment, a calibration curve was used for concentration calculation, but a table in which voltage values and concentration are correlated may be used in place of a calibration curve.

5. Other Embodiments—1

Step **S13** in FIG. **7** is merely an example of processing that reduces the effect of temperature on concentration measurement results. Thus, step **S13** can be replaced by some other processing. The open circuit voltage is an example of voltage that allows electrons to be accumulated in a mediator, but any other voltage with which the effect of electron accumulation can be obtained may be applied instead of an open circuit voltage.

For example, as shown in FIG. **8**, a step **S23** may be executed instead of step **S13**. In step **S23**, a voltage that is lower than the measurement voltage V_{mes} is applied between the working electrode **11** and the counter electrode **12**.

The "voltage that is lower than the measurement voltage V_{mes}" may be any voltage with which electrons can be accumulated in a mediator. For instance, when the measurement voltage V_{mes} is a voltage with positive polarity, the voltage applied in step **S23** may be voltage with positive polarity (FIG. **10**B), or may be 0 V (FIG. **10**C), or may be voltage with an inverse polarity, that is, a negative polarity (FIG. **10**D). More specifically, when the measurement voltage V_{mes} is 250 mV, the voltage applied in step **S23** may be set to about −200 to 150 mV.

A state in which "electrons are accumulated in a mediator" means a state in which no electrons are transferred from the mediator to the electrodes, or very few are transferred.

6. Other Embodiments—2

Steps **S13** and **S23** should be executed prior to the acquisition of a current value (steps **S15** and **S25**). Another voltage application step may be executed before or after steps **S13** and **S23**.

For example, as shown in FIG. **9**, another open circuit voltage application step **S33** may be executed prior to a step **S34** that corresponds to the above-mentioned step **S23**. There are no particular restrictions on the amount of applied voltage in this step **S33** (which could be called a third voltage application step), and may be larger than the measurement voltage V_{mes}.

In addition to the embodiment shown in FIG. **9**, voltage may be applied in the following combinations and orders.

(1) Third voltage application step/open circuit voltage application step/measurement voltage application step

(2) Third voltage application step/open circuit voltage application step/low voltage application step/measurement voltage application step

(3) Open circuit voltage application step/low voltage application step/measurement voltage application step

In all of these combinations, the low voltage application step may include two or more voltage application steps of mutually different voltage values. Also, in all of these combinations, the open circuit voltage application step and the low voltage application step may be switched around.

The time "0" in FIGS. **10**A to **10**D may the point at which the introduction of a sample is detected, or may be the point at which a specific length of time has elapsed since this detection. Also, the duration of applying the open circuit voltage, the duration of applying the low voltage, or the combined duration thereof is preferably 0.5 to 10 seconds. For example, it may be set to about 2 to 5 seconds.

As is clear from the description of the above embodiments, the computer **306** and the reference voltage source **305** function as a first voltage applicator for applying the measurement voltage V_{mes} (first voltage) between the working electrode **11** and the counter electrode **12**, and a second voltage applicator for applying a second voltage (open circuit voltage, low voltage) prior to the application of the first voltage.

Furthermore, in the above embodiments, a single reference voltage source **305** applies different voltages to the electrodes under the control of the computer **306**, but in another constitution, the measurement device **101** may have two or more voltage sources.

Also, the computer **306** functions as a concentration measurement section for measuring the concentration of analyte.

7. Summary

The constitutions discussed in the different sections above can be variously combined. Specifically, the embodiments given above can be rephrased as follows.

1)

A biosensor system with which the concentration of an analyte in a liquid sample is measured using a redox enzyme and an electron-transfer mediator, said biosensor system comprising a sensor chip comprising a capillary into which a liquid sample is introduced, whose height is less than the maximum value of the sum of the diffusion distance of the electron-transfer mediator and the diffusion distance of the analyte at the upper limit of the measurement guaranteed temperature of the biosensor system, a plurality of electrodes disposed within the capillary, and a reagent layer that is disposed within the capillary and includes the electron-transfer mediator; a first voltage applicator that applies a first voltage to the electrodes; a concentration measurement section that measures the concentration of the analyte on the basis of the value of the current flowing through the liquid sample during the first voltage application; and a second voltage applicator that applies a second voltage to the electrodes prior to the application of the first voltage, so that the effect of the temperature of the liquid sample on the measurement results of the concentration measurement section will be diminished.

2)

The biosensor system according to 1) above, wherein the height of the capillary of the sensor chip is less than the maximum value of the sum of the diffusion distance of the electron-transfer mediator and the diffusion distance of the analyte, found from the lower limit of the measurement guaranteed temperature of the biosensor system.

3)

The biosensor system according to 1) or 2) above, wherein the height of the capillary of the sensor chip is set on the basis of the diffusion distances of the electron-transfer mediator and the analyte, each expressed by the following formula (i):

[First Mathematical Formula]

$$d=\sqrt{zDt} \quad \text{(i)}$$

(where d is the diffusion distance, z is an arbitrarily selected constant, D is a diffusion coefficient, and t is time).

4)

The biosensor system according to 3) above,

wherein the constant z in the above Formula (i) satisfies $1 \leq z \leq 4$.

5)

The biosensor system according to any of 1) to 4) above, wherein the second voltage applicator accumulates electrons in the electron-transfer mediator by applying the second voltage.

6)

The biosensor system according to any of 1) to 5) above, wherein the second voltage applicator applies an open circuit voltage as the second voltage.

7)

The biosensor system according to any of 1) to 6) above, wherein the first voltage applicator applies voltage of positive polarity as the first voltage, and the second voltage applicator applies voltage that is lower than the first voltage as the second voltage.

8)

The biosensor system according to any of 1) to 7) above, wherein the concentration measurement section has a calibration curve or table that correlates the current value and the analyte concentration, and calculates the analyte concentration on the basis of the same calibration curve or table even if the temperature of the liquid sample should fluctuate.

9)

The biosensor system according to any of 1) to 8) above, wherein the concentration measurement section measures the analyte concentration on the basis of the current value at a point when no more than 10 seconds have elapsed since the start of the application of the second voltage, and the height of the capillary of the sensor chip is no more than 90 μm.

10)

The biosensor system according to any of 1) to 9), wherein the electrodes are disposed on two faces that are mutually opposite in the height direction of the capillary.

11)

A method for measuring the concentration of an analyte in a liquid sample using a redox enzyme or an electron-transfer mediator, which is executed by a biosensor system having a sensor chip comprising a capillary into which a liquid sample is introduced, whose height is less than the maximum value of the sum of the diffusion distance of the electron-transfer mediator and the diffusion distance of the analyte at the upper limit of the measurement guaranteed temperature of the biosensor system, a plurality of electrodes disposed within the capillary, and a reagent layer that is disposed within the capillary and includes the electron-transfer mediator, said measurement method comprising a first voltage application step of applying a first voltage to the electrodes, a current detection step of detecting the value of current flowing through the liquid sample during the application of the first voltage, a concentration measurement step of measuring the concentration of the analyte on the basis of the current value, and a second voltage application step of applying a second voltage to the electrodes prior to the detection of the current value, so that the temperature of the liquid sample will have less effect on the measurement results of the concentration measurement section.

12)

The measurement method according to 11) above, wherein the second voltage is set such that electrons will be accumulated in the electron-transfer mediator by the application of the second voltage.

13)

The measurement method according to 11) or 12), wherein the average molecular weight is an open circuit voltage.

14)

The measurement method according to any of 11) to 13) above, wherein the first voltage is a voltage of positive polarity, and the second voltage is a voltage that is lower than the first voltage.

15)

The measurement method according to any of 11) to 14) above, wherein the concentration measurement step includes a calculation step of using a calibration curve or table that correlates the current value and the analyte concentration, and calculating the analyte concentration on the basis of the same calibration curve or table even if the temperature of the liquid sample should fluctuate.

16)

The measurement method according to any of 11) to 15) above, wherein the height of the capillary of the sensor chip is no more than 90 μm, and in the concentration measurement step, the concentration of the analyte is measured on the basis of the current value at a point when no more than 10 seconds have elapsed since the start of the application of the second voltage.

EXPERIMENT EXAMPLES

The present invention will now be described in more specific terms through experiment examples.

The above-mentioned biosensor system **100** was used in the following experiment examples. The sensor chip **200** shown in FIGS. **2**, **3**, and **5**A was used as the sensor chip. The sensor chip **200** is constituted as follows.

The capillary **40** was designed so that it was 1.2 mm wide, 4.0 mm long (deep), and 33 to 150 μm high. The height H was confirmed by slicing the sensor chip **200** and using a microscope of measure the distance from the working electrode **11** to the ceiling of the capillary **40** (the inner face of the cover **203**).

Polyethylene terephthalate was used for the insulated board **201**. The electrodes **11** to **13** were each formed by vapor depositing palladium on the insulated board **201**, and making slits with a laser so that the surface area of the working electrode **11** inside the capillary **40** was 1.0 mm^2, and the surface area of the counter electrode **12** inside the capillary **40** was 1.2 mm^2.

The reagent layer **20** was formed as follows. Glucose dehydrogenase, potassium ferricyanide (made by Kanto Chemical), and taurine (made by Nakalai Tesque) were used. An aqueous solution was prepared by dissolving glucose dehydrogenase so that the glucose dehydrogenase concentration in the reagent layer **20** would be 2.0 U/sensor chip. The potassium ferricyanide and the taurine were dissolved in this aqueous solution in amounts of 1.7 wt % and 1.0 wt %, respectively, to obtain a reagent solution. This reagent solution was applied over the insulated board **201**, and the coating was dried in an atmosphere with a humidity of 45% and a temperature of 21° C.

In the following experiment examples, unless otherwise specified, a time of "0" on the graph is the point when the introduction of a sample was detected. Also, the temperature in the following experiment examples is the air temperature of the measurement environment. Blood adjusted to a specific glucose value was used as the sample to be measured.

Experiment Example 1

In this experiment example, the same processing as in FIG. **7** was performed with the above-mentioned biosensor system **100**, except that step **S13** was omitted. That is, steps **S11**, **S12**, and **S14** to **S16** in FIG. **7** were performed. More specifically, after step **S12**, a constant voltage of 250 mV was applied, and the response current value (sometimes referred to simply as "current value") was measured. The current value for each sensor chip was measured using sensor chips with different heights H of the capillary **40**. More specifically, the height H of the capillary **40** was either 150 μm, 100 μm, 59 μm, or 33 μm.

FIGS. **11**A to **11**D show the results of measuring current value using blood with a glucose concentration of 100 mg/dL (deciliter). FIGS. **13**A to **13**D show the results of measuring current value using blood with a glucose concentration of 400 mg/dL (deciliter). FIG. **12**A and FIGS. **11**A to **11**D are graphs of the current value at a point when 8 seconds have elapsed. FIG. **12**B is a graph of the variance in the current value at various temperatures, when the current value at 21° C. in FIG. **12**A was 0%.

As shown in FIGS. **11**A and **11**B and FIGS. **13**A and **13**B, when the height H is high, the current value will be large under high temperature conditions and will be small under low temperature conditions regardless of the measurement time (the elapsed time after the start of the reaction).

Meanwhile, as shown in FIGS. **11**C and **11**D and FIGS. **13**C and **13**D, when the height H is low (59 μm or 33 μm), a larger current value was measured under high temperature conditions than under low temperature conditions while the measurement time was short, but when the measurement time was longer, the a larger current value was measured under low temperature conditions than under high temperature conditions. The reason for this inversion seems to be that with a finite diffusion system, under high temperature conditions more of the substrate (glucose) is consumed in a short period, so the substrate is used up over time, but under low temperature conditions there is substrate left over.

Because this inversion occurs, as shown in FIGS. **12**A and **12**B and FIGS. **14**A and **14**B, in this experiment example there was a large variance in the current value when the temperature changed even when the height H was 33 μm, that is, when the height H was low.

Experiment Example 2

The measurement results for current value in Experiment Example 1 were integrated every 0.1 second to calculate the amount of charge. The results are shown in FIGS. **15**A to **15**D and FIGS. **17**A to **17**D. FIGS. **15**A to **15**D correspond to FIGS. **11**A to **11**D, and FIGS. **17**A to **17**D correspond to FIGS. **13**A to **13**D. FIGS. **16**A and **18**A are graphs of the amount of charge after 8 seconds have elapsed in FIGS. **15**A to **15**D and FIGS. **17**A to **17**D, respectively, and FIGS. **16**B and **18**B are graphs of the variance in the amount of charge due to temperature in FIGS. **16**A and **18**A, respectively.

As shown in these graphs, even if the height H was low, there was a large amount of variance in the amount of charge when a constant voltage was applied.

Experiment Example 3

The response current value was measured with the measurement voltage in step **S14** set at 250 mV and the period in which the applied voltage in step **S13** in FIG. **7** was an open circuit voltage (open). The conditions other than voltage, namely, the height H of the capillary, the temperature conditions, the glucose concentration of the sample, and so forth, were the same as the conditions in Experiment Example 1.

FIGS. **19**A to **19**D show the measurement results for current value when blood with a glucose concentration of 100 mg/dL (deciliter) was used as the sample. As shown in FIGS. **11**A to **11**D, the lower was the height of the capillary **40**, the less variance there was in the measurement results due to environment temperature. In particular, there was little variance when the height H was 59 μm or less, and variance was least at 33 μm.

FIG. **20**A is a graph of the current value at a point when 8 seconds had elapsed in FIGS. **19**A to **19**D (a point when 3 seconds had elapsed after the start of the voltage application of 250 mV). FIG. **20**B is a graph of the variance in the current value at various temperatures when the current value at 21° C. in FIG. **20**A was used as a reference value (0%).

As shown in FIGS. **20**A and **20**B, when the height H is 59 μm, the variance due to temperature was kept to less than ±20%. When the height H was 33 μm, the variance was kept to let than ±10%.

The same experiment was conducted using a sample in which the glucose concentration was 400 mg/dL. As shown in FIGS. **21**A to **21**D and FIGS. **22**A to **22**B, even when the glucose concentration in the sample was high, the variance

was kept small when the height H was 59 μm or less, and particularly when it was 33 μm.

As discussed above, if the height H of the capillary is merely reduced, inversion will occur between the current value at high temperature and the current value at low temperature as the measurement time passes, and variance in the current value due to differences in temperature will not be suppressed.

In contrast, in this experiment example, the mediator is maintained in a state in which no electrons are transmitted to the working electrode **11** inside the capillary **40**, by having the applied voltage be open circuit voltage for 5 seconds after the start of the enzyme reaction. Since the enzyme reaction proceeds during this time as well, electrons are accumulated in the mediator. After this, the measurement voltage V_{mes} is applied and the concentration measured at the point when electrons were accumulated. As a result, the current value during concentration measurement is the sum of adding the amount of reaction during the application of the open circuit voltage to the amount of reaction during the application of the measurement voltage V_{mes}. As a result, it is believed that fluctuation in the measured value caused by the environment temperature during measurement was kept small.

Experiment Example 4

In this experiment example, it was confirmed that the same effect as in Experiment Example 3 can be obtained even when the open circuit voltage is applied for a different length of time. In this experiment example, the duration of application of the open circuit voltage was 1.5 seconds or 3 seconds. Also, the glucose concentration was 40 mg/dL, 155 mg/dL, 345 mg/dL, or 600 mg/dL. In FIGS. **23**A to **23**D, FIGS. **24**A to **24**D, FIGS. **25**A to **25**D, and FIGS. **26**A to **26**D, the duration of application of the open circuit voltage is 1.5 seconds. In FIGS. **28**A to **28**D, FIGS. **29**A to **29**D, FIGS. **30**A to **30**D, and FIGS. **31**A to **31**D, the duration of application of the open circuit voltage is 3 seconds. In all of these drawings, the operation that was carried out is the same except that the glucose concentration is different.

As shown in FIGS. **23**A to **23**D, FIGS. **24**A to **24**D, FIGS. **25**A to **25**D, FIGS. **26**A to **26**D, FIGS. **28**A to **28**D, FIGS. **29**A to **29**D, FIGS. **30**A to **30**D, and FIGS. **31**A to **31**D, even when there is a change in the glucose concentration and/or the open circuit voltage application duration, variance in the current value due to temperature was small when the height H was 59 μm or less, and particularly when it was 33 μm.

Also, as shown in FIGS. **27**A to **27**D, when the height H was 59 μm or less, the current value was not affected greatly by temperature. That is, accurate measurement results were obtained, with little error due to temperature. In particular, variance was extremely small when the height was 33 μm. If variance is small, then even if the temperature is different, the concentration can be calculated from a single calibration curve. As shown in FIGS. **32**A to **32**D, the same results were observed for the current value at the point when 7 seconds had elapsed in FIG. **29** (the measurement results when the open circuit voltage application duration was 3 seconds and the glucose concentration was 155 mg/dL).

Experiment Example 5

In the following Experiment Examples 5 to 9, the glucose concentration is 100 mg/dL.

In Experiment Example 5, the response current value was measured when the height H of the sensor chip is 150, 104, 90, 82, 69, 59, 49, or 33 μm, the duration of application of the open circuit voltage was 0, 1, 1.5, 2, 3, 4, 5, 6, or 7 seconds, and the 250 mV measurement voltage was applied after the application of the open circuit voltage.

When FIGS. **33**A to **34**D, which show the results when no open circuit voltage was applied (when the application duration was 0 seconds), are compared to FIGS. **35**A to **36**D, which show the results when an open circuit voltage was applied, it can be seen that variance in the current value due to temperature was kept smaller when the open circuit voltage was applied. This effect is more pronounced when the open circuit voltage was applied for at least 1.5 seconds, and even more so when the application was for at least 2 seconds.

Data is shown in the drawings for when the open circuit voltage was applied for up to 5 seconds, but variance in the current value due to temperature was similarly kept small when the application length was 6 or 7 seconds.

Experiment Example 6

The height H of the sensor chip was 150, 104, 90, 82, 69, 59, 49, or 33 μm. The duration of application of the open circuit voltage was 0 or 2 seconds. The response current value was measured for when the 250 mV measurement voltage was applied after the application of the open circuit voltage.

Under the various conditions, the current value was measured at 5° C., 14° C., 21° C., 30° C., and 38° C., and the discrepancy (variance) in the result obtained at each temperature from the measurement result at 21° C. was calculated. In FIGS. **47**A to **50**D, the discrepancy when the height H is 150 μm is expressed by a broken line, and the discrepancy when the height H is 104, 90, 82, 69, 59, 49, or 33 μm is expressed by a solid line.

That is, the solid-line curve at the top in FIG. **49**A shows how much the current value obtained when a measurement voltage of 250 mV was applied after the application of an open circuit voltage for 2 seconds (open duration) at 38° C., with a sensor chip having a height H of 104 μm, deviates from the current value measured at 21° C. (measured under the same conditions except for the temperature). That is, the closer the solid line is to the 0% horizontal axis, the smaller is the variance. The broken line at the top in this same drawing shows how much the current value measured at a height H of 150 μm and 38° C. deviates from the current value measured at 21° C.

As shown in FIGS. **47**A to **50**C, when the open circuit voltage application duration was 2 seconds, the variance due to temperature was kept smaller than when the duration was 0 seconds.

As shown in FIGS. **49**A to **49**D and FIGS. **50**A to **50**C, the variance in current value when the height H is 104 μm is quite different from the variance in current value when the height H is 150 μm (FIG. **49**A). In contrast, when the height H is 90 μm or less, the variance in current value due to temperature was kept smaller than when the height H was 104 μm (FIG. **49**B, etc.). Specifically, the height H of the capillary is preferably 90 μm or less.

Although not shown in the data graphs, the variance was similarly kept small when the open circuit voltage application duration was 3 to 5 seconds.

Experiment Example 7

In this experiment example, a measurement voltage of 250 mV was applied after a voltage of 100 mV had been

applied for 3 seconds to sensor chips of different heights H. The heights H were 150, 104, 90, 82, 69, 59, 49, and 33 μm.

As shown in FIGS. **51**A to **51**D and FIGS. **52**A to **52**D, this experiment example makes it clear that there is still a variance suppression effect even when a voltage that is lower than the measurement voltage is applied instead of an open circuit voltage. The variance suppression effect was particularly pronounced when the height H was 59 μm or less.

Experiment Example 8

In this experiment example, a measurement voltage of 250 mV was applied after a voltage of 0 mV had been applied for 3 seconds to sensor chips of different heights H. The heights H were the same as in Experiment Example 7.

As shown in FIGS. **53**A to **53**D and FIGS. **54**A to **54**D, there is still a variance suppression effect even when a voltage of 0 mV is applied instead of an open circuit voltage. The variance suppression effect was particularly pronounced when the height H was 59 μm or less.

Experiment Example 9

In this experiment example, a measurement voltage of 250 mV was applied after a voltage of 250 mV had first been applied for 1 second to sensor chips of different heights H, followed by the application of an open circuit voltage for 2 seconds. The heights H were the same as in Experiment Example 7.

As shown in FIGS. **55**A to **55**D and FIGS. **56**A to **56**D, there is still a variance suppression effect even when a closed circuit voltage is applied prior to the application of an open circuit voltage. The variance suppression effect was particularly pronounced when the height H was 59 μm or less.

Furthermore, it was confirmed that if an open circuit voltage is applied and/or a voltage lower than the measurement voltage is applied after the application of a voltage higher than the measurement voltage, there was less variance due to temperature in the current value obtained when measurement voltage was applied subsequently to this.

INDUSTRIAL APPLICABILITY

The sensor chip, the biosensor system comprising this sensor chip, the method for measuring the temperature of a biological sample, and the concentration measurement method of the present invention all have the effect of allowing concentration measurement error attributable to temperature to be effectively suppressed, and therefore can be widely applied in various fields that require more accurate measurement.

REFERENCE SIGNS LIST

11 working electrode (electrode)
12 counter electrode (electrode)
13 detection electrode
16 air vent
17 introduction port
20 reagent layer
40 capillary
100 biosensor system
101 measurement device
102 mounting opening
103 display section
200 sensor chip
201 insulated board
202 spacer
203 cover
204 cut-out
300 control circuit
301*a*, **301***b*, **301***c* connector
302 switching circuit
303 current/voltage conversion circuit
304 analog/digital (A/D) conversion circuit
305 reference voltage source (first voltage applicator, second voltage applicator)
306 computer (concentration measurement section, first voltage applicator, second voltage applicator)

The invention claimed is:

1. A biosensor system, with which the concentration of an analyte in a liquid sample is measured using a redox enzyme and a potassium ferricyanide as an electron-transfer mediator, said biosensor system comprising:

a sensor chip having a capillary into which a liquid sample is introduced, a plurality of electrodes disposed within the capillary, and a reagent layer that is disposed within the capillary and includes the electron-transfer mediator;

the capillary having a height less than the maximum value of the sum of the diffusion distance of the electron-transfer mediator and the diffusion distance of the analyte at an upper temperature limit for which the biosensor system is functional;

the plurality of electrodes including a working electrode and a counter electrode; and

the plurality of electrodes are disposed so as to be opposite each other in a horizontal plane;

a voltage applicator that

applies a measurement voltage to the working electrode and the counter electrode,

applies a second voltage of positive polarity to the working electrode and the counter electrode prior to the application of the measurement voltage, so that the effect of the temperature of the liquid sample on the measurement results of the concentration measurement section will be diminished, and

applies a first voltage to the working electrode and the counter electrode prior to the application of the second voltage,

wherein the second voltage is positive with respect to a ground used when applying the measurement voltage, and

wherein the second voltage is lower than the measurement voltage;

a concentration measurement section that measures the concentration of the analyte on the basis of the value of the current flowing through the liquid sample during the measurement voltage application; and

wherein the height of the capillary of the sensor chip is the distance from the working electrode to an opposite face from the working electrode, and the height of the capillary of the sensor chip is between 49 and 90 μm.

2. The biosensor system according to claim **1**,

wherein the height of the capillary of the sensor chip is less than the maximum value of the sum of the diffusion distance of the electron-transfer mediator and the diffusion distance of the analyte, found from a lower temperature limit for which biosensor system is functional.

3. The biosensor system according to claim **1**,

wherein the voltage applicator accumulates electrons in the electron-transfer mediator by applying the second voltage.

4. The biosensor system according to claim 1,
wherein the voltage applicator applies an open circuit voltage as the second voltage.

5. The biosensor system according to claim 1,
wherein the concentration measurement section has a calibration curve or table that correlates the current value and the analyte concentration, and calculates the analyte concentration on the basis of the same calibration curve or table even if the temperature of the liquid sample should fluctuate.

6. The biosensor system according to claim 1,
wherein the concentration measurement section measures the analyte concentration on the basis of the current value at a point when no more than 10 seconds have elapsed since the start of the application of the second voltage.

7. The biosensor system according to claim 1,
wherein the electrodes are disposed on two faces that are mutually opposite in the height direction of the capillary.

8. The biosensor system according to claim 1,
wherein the second voltage is smaller than the measurement voltage, and
the first voltage is bigger than the second voltage.

9. The biosensor system according to claim 1,
wherein the height of the capillary of the sensor chip is between 49 and 59 μm.

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